TECHNOLOGY DEPARTMENT

PUBLIC LIBRARY
FEB 18 1949

Journal of
THE CHEMICAL SOCIETY

Committee of Publication :

Chairman : Sir Cyril Hinshelwood, M.A., Sc.D., D.Sc., F.R.S.

Sir Wallace Akers, C.B.E., B.A., F.R.I.C.
M. P. Applebey, M.B.E., M.A., D.Sc.
W. Baker, M.A., D.Sc., F.R.S., F.R.I.C.
G. M. Bennett, C.B., M.A., Sc.D., F.R.S., F.R.I.C.
F. Bergel, D.Phil.Nat., Ph.D., D.Sc., F.R.I.C.
E. G. Cox, D.Sc., F.Inst.P., F.R.I.C.
M. G. Evans, D.Sc., F.R.S.
C. S. Gibson, O.B.E., M.A., Sc.D., F.R.S.
D. L. Hammick, M.A.
Sir Ian Heilbron, D.S.O., D.Sc., LL.D., F.R.S.
D. H. Hey, Ph.D., D.Sc., F.R.I.C.
C. K. Ingold, D.Sc., F.R.S., F.R.I.C.
D. J. G. Ives, D.Sc., A.R.C.S., F.R.I.C.
E. R. H. Jones, D.Sc., F.R.I.C.
A. King, C.B.E., D.Sc., A.R.C.S.
F. E. King, M.A., D.Sc., Ph.D., D.Phil.
G. A. R. Kon, M.A., D.Sc., F.R.S.
R. P. Linstead, C.B.E., M.A., Ph.D., D.Sc., F.R.S.
H. W. Melville, Ph.D., D.Sc., F.R.S.
R. G. W. Norrish, B.A., Sc.D., F.R.S.
S. Peat, Ph.D., D.Sc., F.R.S.
S. G. P. Plant, D.Phil., M.A., B.Sc.
H. Raistrick, Sc.D., F.R.S., F.R.I.C.
E. K. Rideal, M.B.E., M.A., D.Sc., Ph.D., F.R.S.
F. L. Rose, B.Sc., Ph.D., F.R.I.C.
B. C. Saunders, M.A., Ph.D., F.R.I.C.
J. L. Simonsen, D.Sc., F.R.S., F.R.I.C.
D. W. G. Style, Ph.D.
S. Sugden, D.Sc., F.R.S., F.R.I.C.
H. W. Thompson, M.A., B.Sc., D.Phil., F.R.S.
A. R. Todd, M.A., D.Phil., D.Sc., F.R.S.
W. Wardlaw, D.Sc., F.R.I.C.
F. G. Young, D.Sc., Ph.D., F.R.I.C.

Editor :

J. E. Driver, M.A., Ph.D., M.Sc., F.R.I.C.

Assistant Editors :

A. D. Mitchell, D.Sc., F.R.I.C.
L. C. Cross, Ph.D., A.R.C.S., F.R.I.C.

Indexer :

Margaret Le Pla, B.Sc.

DECEMBER, 1948

Subscription rate to non-Fellows £3 15s. 0d. per annum post free.

LONDON: THE CHEMICAL SOCIETY, BURLINGTON HOUSE, W.1

THE CHEMICAL SOCIETY

PATRON :

HIS MAJESTY THE KING

President :

SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.S.

Vice-Presidents

who have filled the office of President :

F. G. DONNAN, C.B.E., D.Sc., LL.D., F.R.S.
SIR NORMAN HAWORTH, Sc.D., LL.D., F.R.S.
SIR CYRIL HINSHELWOOD, M.A., Sc.D., D.Sc., F.R.S.
W. H. MILLS, M.A., Sc.D., F.R.S.
SIR ROBERT ROBINSON, M.A., D.Sc., LL.D., P.R.S.
N. V. SIDGWICK, C.B.E., D.Sc., LL.D., F.R.S.

Vice-Presidents :

R. P. BELL, M.A., B.Sc., F.R.S.
G. M. BENNETT, C.B., M.A., Sc.D., F.R.S., F.R.I.C.
J. KENYON, D.Sc., F.R.S., F.R.I.C.
R. P. LINSTEAD, C.B.E., M.A., Ph.D., D.Sc., F.R.S.
S. SUGDEN, D.Sc., F.R.S., F.R.I.C.
A. R. TODD, M.A., D.Phil., D.Sc., F.R.S.

Treasurer :

SIR WALLACE AKERS, C.B.E., B.A., F.R.I.C.

Secretaries :

J. L. SIMONSEN, D.Sc., F.R.S., F.R.I.C.
D. H. HEY, Ph.D., D.Sc., F.R.I.C.
A. KING, C.B.E., D.Sc., A.R.C.S.

Ordinary Members of Council:

L. L. BIRCUMSHAW, M.A., D.Sc.
G. R. CLEMO, D.Phil., D.Sc., Ph.D., F.R.S.
A. H. COOK, Ph.D., D.Sc., F.R.I.C., D.I.C.
F. S. DAINTON, M.A., Ph.D.
J. F. J. DIPPY, Ph.D., D.Sc., F.R.I.C.
G. M. DYSON, M.A., Ph.D., B.Sc., F.R.I.C.
A. E. GILLAM, D.Sc., F.R.I.C.
F. R. GOSS, D.Sc., Ph.D., A.R.C.S., F.R.I.C.
FRANCES M. HAMER, M.A., Sc.D., D.Sc., F.R.I.C.
S. H. HARPER, D.Sc., Ph.D., A.R.C.S.
D. W. HILL, Ph.D., D.Sc., F.R.I.C.
A. MCGOOKIN, D.Sc., Ph.D., A.R.I.C.
T. MALKIN, Ph.D., D.Sc., F.R.I.C.
F. G. MANN, Sc.D., D.Sc., F.R.S., F.R.I.C.
H. W. MELVILLE, Ph.D., D.Sc., F.R.S.
E. G. V. PERCIVAL, Ph.D., D.Sc., F.R.I.C.
H. N. RYDON, D.Sc., Ph.D., D.Phil., A.R.C.S., F.R.I.C.
F. S. SPRING, Ph.D., D.Sc., F.R.I.C.
L. E. SUTTON, M.A., D.Phil.
J. WALKER, Ph.D., D.Phil., D.Sc.
T. S. WHEELER, Ph.D., D.Sc., F.R.I.C., M.I.Chem.E.

Ex-Officio Members of Council:

H. E. COX, D.Sc., Ph.D., F.R.I.C. (*Chairman of the Joint Library Committee*).
L. H. LAMPITT, D.Sc., F.R.I.C. (*Chairman of the Bureau of Abstracts*).
E. K. RIDEAL, M.B.E., M.A., D.Sc., Ph.D., F.R.S. (*Chairman of the Chemical Council*).

General Secretary :

J. R. RUCK KEENE, M.B.E., B.A.

Librarian :

A. E. CUMMINS.

Telephone Numbers : Regent 1675/6

CONTENTS.

PAPERS COMMUNICATED TO THE CHEMICAL SOCIETY.

General, Physical, and Inorganic.

PAGE

413. The Measurement of Gas Solubilities.
By T. J. MORRISON and F. BILLETT 2033

430. Chemistry of the Inter-halogen Compounds. Part I. The Reaction of Bromine Trifluoride with Metallic Halides.
By A. G. SHARPE and H. J. EMELÉUS 2135

435. Syntheses and Reactions of Mordenite.
By R. M. BARRER 2158

436. Colour Reactions and Adsorption of Some Aluminosilicates.
By H. WEIL-MALHERBE and J. WEISS 2164

442. The Preparation and Reactions of Carbonyl and Sulphuryl Fluorides and Chlorofluorides.
By H. J. EMELÉUS and J. F. WOOD 2183

443. The Reaction of Bromine Trifluoride and Iodine Pentafluoride with Carbon Tetrachloride, Tetrabromide, and Tetraiodide and with Tetraiodoethylene.
By A. A. BANKS, H. J. EMELÉUS, R. N. HASZELDINE, and V. KERRIGAN . . 2188

453. The Thermal Decomposition of *n*-Hexane.
By R. G. PARTINGTON and C. J. DANBY 2226

462. The Absorption of Antibacterial Substances (2 : 8-Diaminoacridine and Methyleneblue) by Cells of *Bact. lactis ærogenes*.
By A. R. PEACOCKE and SIR CYRIL HINSHELWOOD 2290

Physical Organic.

416. Mechanism of Elimination Reactions. Part VI. Introduction to a Group of Papers. Unimolecular Olefin Formation from *tert.*-Butyl- and *tert.*-Amylsulphonium Salts.
By K. A. COOPER, E. D. HUGHES, C. K. INGOLD, and B. J. MACNULTY . . 2038

417. Mechanism of Elimination Reactions. Part VII. Solvent Effects on Rates and Product-proportions in Uni- and Bi-molecular Substitution and Elimination Reactions of Alkyl Halides and Sulphonium Salts in Hydroxylic Solvents.
By K. A. COOPER, M. L. DHAR, E. D. HUGHES, C. K. INGOLD, B. J. MACNULTY, and L. I. WOOLF 2043

418. Mechanism of Elimination Reactions. Part VIII. Temperature Effects on Rates and Product-proportions in Uni- and Bi-molecular Substitution and Elimination Reactions of Alkyl Halides and Sulphonium Salts in Hydroxylic Solvents.
By K. A. COOPER, E. D. HUGHES, C. K. INGOLD, G. A. MAW, and B. J. MACNULTY 2049

419. Mechanism of Elimination Reactions. Part IX. Kinetics of Olefin Elimination from *n*-Propyl, *n*-Butyl, *n*-Amyl, and *iso*Butyl Bromides in Alkaline Alcoholic Media.
By M. L. DHAR, E. D. HUGHES, C. K. INGOLD, and S. MASTERMAN . . . 2055

420. Mechanism of Elimination Reactions. Part X. Kinetics of Olefin Elimination from *iso*Propyl, *sec.*-Butyl, 2-*n*-Amyl, and 3-*n*-Amyl Bromides in Acidic and Alkaline Alcoholic Media.
By M. L. DHAR, E. D. HUGHES, and C. K. INGOLD 2058

421. Mechanism of Elimination Reactions. Part XI. Kinetics of Olefin Elimination from *tert.*-Butyl and *tert.*-Amyl Bromides in Acidic and Alkaline Alcoholic Media.
By M. L. DHAR, E. D. HUGHES, and C. K. INGOLD 2065

422. Mechanism of Elimination Reactions. Part XII. Kinetics of Olefin Eliminations from Ethyl-, *n*-Propyl-, *n*-Butyl, *iso*Butyl-, and 2-Phenylethyl-dimethylsulphonium Salts in Alkaline Alcoholic Media.
By E. D. HUGHES, C. K. INGOLD, and G. A. MAW 2072

423. Mechanism of Elimination Reactions. Part XIII. Kinetics of Olefin Elimination from *iso*Propyl-, *sec.*-Butyl-, and 1-Phenylethyl-dimethylsulphonium Salts in Alkaline Alcoholic Media.
By E. D. HUGHES, C. K. INGOLD, G. A. MAW, and L. I. WOOLF. . . . 2077

PAGE

424. Mechanism of Elimination Reactions. Part XIV. Kinetics of Olefin Elimination from *tert.*-Butyl- and *tert.*-Amyl-dimethylsulphonium Salts in Alkaline and Acidic Alcoholic Media.
By E. D. Hughes, C. K. Ingold, and L. I. Woolf 2084

425. Mechanism of Elimination Reactions. Part XV. Olefin Elimination from *sec.*-*iso*Amyl Iodide and from the *sec.*-*iso*Amyl-dimethylsulphonium Ion.
By E. D. Hughes, C. K. Ingold, and A. M. M. Mandour 2090

426. Mechanism of Elimination Reactions. Part XVI. Constitutional Influences in Elimination. A General Discussion.
By M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw, and L. I. Woolf 2093

427. The Kinetics of Photochemical Oxidation with Dichromate: The Oxidation of Glycerol.
By K. Weber and S. Ašperger 2119

454. The Propagation of Reaction Chains in the Polymerisation of Styrene.
By J. W. Menary, A. R. Ubbelohde, and M. J. Wright. 2232

455. The Strength of Heterocyclic Bases.
By Adrien Albert, Reginald Goldacre, and John Phillips. . . . 2240

459. Infra-red Spectroscopic Measurements of Substituted Pyrimidines. Part I. The Presence of Hydrogen Bonding in 4-Triacetyl-D-xylosidaminopyrimidines.
By I. A. Brownlie, G. B. B. M. Sutherland, and A. R. Todd . . . 2265

460. The Dipole Moments of *N*- and *C*-Substituted Sydnones.
By J. C. Earl, Eleanor M. W. Leake, and R. J. W. Le Fèvre . . . 2269

Organic.

405. The Constitution of Evodione.
By S. E. Wright 2005

406. Polyquinolyls.
By S. G. Waley 2008

407. Synthesis of Piperidine Derivatives. Part II. Aryldecahydroquinolines.
By G. M. Badger, J. W. Cook, and Thomas Walker 2011

408. Reactions of Polynitro-aromatic Compounds with Alkaline Sulphides. Part I. Aryl Monosulphide Formation by Interaction of Sodium Thioaryloxides with Polynitro-aromatic Compounds containing Labile Nitro-groups.
By Herbert H. Hodgson and Edward R. Ward 2017

409. The Nitration of 4-Aminoquinoline.
By J. C. E. Simpson and P. H. Wright 2023

410. Some *Bz*-Substituted-3-nitroquinolines.
By J. S. Morley and J. C. E. Simpson 2024

411. Studies in the Azole Series. Part IX. The Interaction of α-Amino-nitriles and Alkyl *iso*Thiocyanates.
By A. H. Cook, J. D. Downer, and Sir Ian Heilbron 2028

412. Studies in the Azole Series. Part X. Some 5-Amino-2-mercapto-4-alkylthiazoles and 2 : 4-Dithio-5-alkylhydantoins.
By A. H. Cook, Sir Ian Heilbron, and E. S. Stern 2031

414. The Chemistry of Ribose and its Derivatives. Part I. Methyl-D-ribofuranoside and the Characterisation of Trimethyl D-Ribofuranose.
By G. R. Barker 2035

415. A Synthesis of 3-Acyl- and 3-Aroyl-*meso*benzanthrones.
By F. Irving and A. W. Johnson 2037

428. Photochemical Reactions. Part XIII. (*a*) Photochemical Reactions of Ethylenes with Phenanthraquinone and with 1 : 2 : 3-Triketones. (*b*) Dimerisation Reactions in Sunlight.
By Alexander Schönberg, Ahmed Mustafa, Mohamed Zaki Barakat, Nazih Latif, Radwan Moubasher, and Akila Mustafa (Mrs. Said) . . . 2126

429. N^1-Sulphanilamides derived from Aminoquinoxalines and Aminomethylquinoxalines.
By Bertie C. Platt and Thomas M. Sharp 2129

431. The Structure of Ginkgetin. Part I. Synthesis of 5 : 8-Dihydroxy-4′-methoxyflavone.
By Wilson Baker and G. F. Flemons 2138

432. Substitution in 3 : 4-Dialkylphenols.
By G. D. Parkes 2143

PAGE

433. Some Heterocyclic Analogues of Stilbenes.
By Daniel M. Brown and George A. R. Kon 2147

434. Some Catalysed Gas-phase Reactions of Aromatic Hydrocarbons. Part IV. The Polymethylbenzenes formed in the Reactions of Dimethyl Ether with Benzene, Toluene, and the Xylenes.
By P. H. Given and D. Ll. Hammick 2154

437. Products of Nitration of Some Derivatives of Dimethylaniline, Auramine, and Crystal-violet.
By S. Galinowski and T. Urbański 2169

438. Alkaloids of *Daphnandra* Species. Part I. Repandine.
By I. R. C. Bick and A. R. Todd 2170

439. Amines containing 2-Halogenoethyl Groups.
By A. F. Childs, L. J. Goldsworthy, G. F. Harding, F. E. King, A. W. Nineham, W. L. Norris, S. G. P. Plant, B. Selton, and A. L. L. Tompsett 2174

440. Some Sulphides containing the 2-Chloroethyl Group.
By L. J. Goldsworthy, G. F. Harding, W. L. Norris, S. G. P. Plant, and B. Selton 2177

441. Compounds containing the 3-Chloroallyl Group.
By A. F. Childs, S. G. P. Plant, A. L. L. Tompsett, and G. A. Weeks . . 2180

444. The Conversion of Sucrose into Pyridazine Derivatives. Part III. Constitutional Studies on the Products of Chlorination of 2 : 6-Dimethyl-3-pyridazone.
By R. F. Homer, Hilda Gregory, and L. F. Wiggins 2191

445. The Conversion of Sucrose into Pyridazine Derivatives. Part IV. Further Sulphanilamides derived from 6-Methyl-3-pyridazone.
By R. F. Homer, Hilda Gregory, W. G. Overend, and L. F. Wiggins . . 2195

446. The Conversion of Sucrose into Pyridazine Derivatives. Part V. Experiments on the Synthesis of 3-Amino-6-methylpyridazine and of its Sulphanilamido-derivative.
By Hilda Gregory, W. G. Overend, and L. F. Wiggins 2199

447. Anhydrides of Polyhydric Alcohols. Part XI. The Action of Phosphorus Tribromide on 1 : 4-3 : 6-Dianhydro-mannitol and -sorbitol. Some New Chloro-derivatives of 1 : 4-3 : 6-Dianhydrosorbitol.
By W. G. Overend, R. Montgomery, and L. F. Wiggins 2201

448. Anhydrides of Polyhydric Alcohols. Part XII. The Reaction between Mannitol and Hydrochloric Acid.
By R. Montgomery and L. F. Wiggins 2204

449. Compounds of Diarylcyanoarsine Type.
By L. J. Goldsworthy, W. H. Hook, J. A. John, S. G. P. Plant, J. Rushton, and L. M. Smith 2208

450. Union of Aryl Nuclei. Part VII. Reactions with Acyl Peroxides.
By D. H. Hey and E. W. Walker 2213

451. Syntheses of Glycosides. Part XIII. Primulaverin.
By D. N. Chaudhury, H. I. King, and Alexander Robertson 2220

452. The Chemistry of the Melanins. Part I. The Synthesis of 5 : 6-Dihydroxyindole and Related Compounds.
By R. J. S. Beer, Kenneth Clarke, H. G. Khorana, and Alexander Robertson 2223

456. The Catechins of Green Tea. Part II.
By A. E. Bradfield and (Miss) M. Penney 2249

457. Furano-compounds. Part VII. A Synthesis of 2 : 3-Dihydropsoralene.
By R. T. Foster, Alexander Robertson, and (in part) Anis Bushra . . 2254

458. Furano-compounds. Part VIII. The Synthesis of *iso*Visnagin and a Partial Synthesis of Visnagin.
By J. R. Clarke, George Glaser, and Alexander Robertson 2260

461. The Autoxidation of Methyl Oleate and Linoleate, and the Decomposition of the Oxidation Products: A Theoretical Discussion.
By G. Philip Gibson 2275

463. The Elbs Persulphate Oxidation of Phenols, and its Adaptation to the Preparation of Monoalkyl Ethers of Quinols.
By Wilson Baker and N. C. Brown 2303

464. Further Studies on the Sydnones.
By Ronald A. Eade and J. Campbell Earl 2307

465. Pectic Substances. Part VIII. The Araban Component of Sugar-beet Pectin.
By E. L. Hirst and J. K. N. Jones 2311

PAGE

466. 2-Amino-1 : 3 : 4-indotriazine. The Reaction between Isatin and Aminoguanidine.
By HAROLD KING and JEAN WRIGHT 2314

NOTES.—The Synthesis of 1 : 3-Dihydroxyphenazine.
By G. R. CLEMO and A. F. DAGLISH 2318

Cinnolines. Part XX. 4-Hydroxy-3-ethylcinnoline and 3-4′-Hydroxy-3′-cinnolyl-*n*-propane-1-carboxylic Acid.
By J. R. KENEFORD and J. C. E. SIMPSON 2318

The Formation of Ketones from Semicarbazones by the Action of Nitrous Acid.
By D. H. HEY and D. S. MORRIS 2319

The Preparation of Certain Urethanes and Their Conversion into *N*-Nitroso-derivatives. Some Chloronitro-compounds of the Type $CRR'Cl{\cdot}CCl(NO_2)R''$.
By A. F. CHILDS, L. J. GOLDSWORTHY, G. F. HARDING, S. G. P. PLANT, and G. A. WEEKS 2320

The Condensation of Chloral with Aryl Cyanides.
By R. F. BATT and D. WOODCOCK 2322

OBITUARY NOTICE 2323

INDEX OF AUTHORS' NAMES.

ALBERT, A., Goldacre, R., and Phillips, J., 2240.
Ašperger, S. See Weber, K.
Badger, G. M., Cook, J. W., and Walker, T., 2011.
Baker, W., and Brown, N. C., 2303.
Baker, W., and Flemons, G. F., 2138.
Banks, A. A., Emeléus, H. J., Haszeldine, R. N., and Kerrigan, V., 2188.
Barakat, M. Z. See Schönberg, A.
Barker, G. R., 2035.
Barrer, R. M., 2158.
Batt, R. F., and Woodcock, D., 2322.
Beer, R. J. S., Clarke, K., Khorana, H. G., and Robertson, A., 2223.
Bick, I. R. C., and Todd, A. R., 2170.
Billett, F. See Morrison, T. J.
Bradfield, A. E., and Penney, (Miss) M., 2249.
Brown, D. M., and Kon, G. A. R., 2147.
Brown, N. C. See Baker, W.
Brownlie, I. A., Sutherland, G. B. B. M., and Todd, A. R., 2265.
Bushra, A. See Foster, R. T.
Chaudhury, D. N., King, H. I., and Robertson, A., 2220.
Childs, A. F., Goldsworthy, L. J., Harding, G. F., King, F. E., Nineham, A. W., Norris, W. L., Plant, S. G. P., Selton, B., and Tompsett, A. L. L., 2174.
Childs, A. F., Goldsworthy, L. J., Harding, G. F., Plant, S. G. P., and Weeks, G. A., 2320.
Childs, A. F., Plant, S. G. P., Tompsett, A. L. L., and Weeks, G. A., 2180.
Clarke, J. R., Glaser, G., and Robertson, A., 2260.
Clarke, K. See Beer, R. J. S.
Clemo, G. R., and Daglish, A. F., 2318.
Cooper, K. A., Dhar, M. L., Hughes, E. D., Ingold, C. K., MacNulty, B. J., and Woolf, L. I., 2043.
Cooper, K. A., Hughes, E. D., Ingold, C. K., and MacNulty, B. J., 2038.
Cooper, K. A., Hughes, E. D., Ingold, C. K., Maw, G. A., and MacNulty, B. J., 2049.
Cook, A. H., Downer, J. D., and Heilbron, Sir I., 2028.
Cook, A. H., Heilbron, Sir I., and Stern, E. S., 2031.
Cook, J. W. See Badger, G. M.
Daglish, A. F. See Clemo, G. R.
Danby, C. J. See Partington, R. G.
Dhar, M. L., Hughes, E. D., and Ingold, C. K., 2058, 2065.
Dhar, M. L., Hughes, E. D., Ingold, C. K., Mandour, A. M. M., Maw, G. A., and Woolf, L. I., 2093.
Dhar, M. L., Hughes, E. D., Ingold, C. K., and Masterman, S., 2055.
Dhar, M. L. See Cooper, K. A.
Downer, J. D. See Cook, A. H.
Eade, R. A., and Earl, J. C., 2307.
Earl, J. C., Leake, E. M. W., and Le Fèvre, R. J. W., 2269.
Earl, J. C. See also Eade, R. A.
Emeléus, H. J., and Wood, J. F., 2183.
Emeléus, H. J. See also Banks, A. A., and Sharpe, A. G
Flemons, G. F. See Baker, W.
Foster, R. T., Robertson, A., and Bushra, A., 2254.
Galinowski, S., and Urbański, T., 2169.
Gibson, G. P., 2275.
Given, P. H., and Hammick, D. Ll., 2154.
Glaser, G. See Clarke, J. R.
Goldacre, R. See Albert, A.
Goldsworthy, L. J., Harding, G. F., Norris, W. L., Plant, S. G. P., and Selton, B., 2177.
Goldsworthy, L. J., Hook, W. H., John, J. A., Plant, S. G. P., Rushton, J., and Smith, L. M., 2208
Goldsworthy, L. J. See also Childs, A. F.
Gregory, (Mrs.) H., Overend, W. G., and Wiggins, L. F., 2199.
Gregory, (Mrs.) H. See also Homer, R. F.
Hammick, D. Ll. See Given, P. H.
Harding, G. F. See Childs, A. F., and Goldsworthy, L. J.
Haszeldine, R. N. See Banks, A. A.
Heilbron, Sir I. See Cook, A. H.
Hey, D. H., and Morris, D. S., 2319.
Hey, D. H., and Walker, E. W., 2213.
Hinshelwood, Sir C. See Peacocke, A. R.
Hirst, E. L., and Jones, J. K. N., 2311.
Hodgson, H. H., and Ward, E. R., 2017.
Homer, R. F., Gregory, (Mrs.) H., Overend, W. G., and Wiggins, L. F., 2195.

Homer, R. F., Gregory, (Mrs.) H., and Wiggins, L. F., 2191.
Hook, W. H. See Goldsworthy, L. J.
Hughes, E. D., Ingold, C. K., and Mandour, A. M. M., 2090.
Hughes, E. D., Ingold, C. K., and Maw, G. A., 2072.
Hughes, E. D., Ingold, C. K., Maw, G. A., and Woolf, L. I., 2077.
Hughes, E. D., Ingold, C. K., and Woolf, L. I., 2084.
Hughes, E. D. See also Cooper, K. A., and Dhar, M. L.
Ingold, C. K. See Cooper, K. A., Dhar, M. L., and Hughes, E. D.
Irving, F., and Johnson, A. W., 2037.
John, J. A. See Goldsworthy, L. J.
Johnson, A. W. See Irving, F.
Jones, J. K. N. See Hirst, E. L.
Keneford, J. R., and Simpson, J. C. E., 2318.
Kerrigan, V. See Banks, A. A.
Khorana, H. G. See Beer, R. J. S.
King, F. E. See Childs, A. F.
King, H., and Wright, J., 2314.
King, H. I. See Chaudhury, D. N.
Kon, G. A. R. See Brown, D. M.
Latif, N. See Schönberg, A.
Leake, E. M. W. See Earl, J. C.
Le Fèvre, R. J. W. See Earl, J. C.
MacNulty, B. J. See Cooper, K. A.
Mandour, A. M. M. See Dhar, M. L., and Hughes, E. D.
Masterman, S. See Dhar, M. L.
Maw, G. A. See Cooper, K. A., Dhar, M. L., and Hughes, E. D.
Menary, J. W., Ubbelohde, A. R., and Wright, M. J., 2232.
Montgomery, R., and Wiggins, L. F., 2204
Montgomery, R. See also Overend, W. G.
Morley, J. S., and Simpson, J. C. E., 2024.
Morris, D. S. See Hey, D. H
Morrison, T. J., and Billett, F., 2033.
Moubasher, R. See Schönberg, A.
Mustafa, A. See Schönberg, A.
Mustafa, Akila. See Schönberg, A.
Nineham, A. W. See Childs, A. F.
Norris, W. L. See Childs, A. F., and Goldsworthy, L. J.
Overend, W. G., Montgomery, R., and Wiggins, L. F., 2201.
Overend, W. G. See also Gregory, (Mrs.) H., and Homer, R. F.
Parkes, G. D., 2143.
Partington, R. G., and Danby, C. J., 2226.
Peacocke, A. R., and Hinshelwood, Sir C., 2290.
Penney, (Miss) M. See Bradfield, A. E.
Phillips, J. See Albert, A.
Plant, S. G. P. See Childs, A. F., and Goldsworthy, L. J.
Platt, B. C., and Sharp, T. M., 2129.
Robertson, A. See Beer, R. J. S., Chaudhury, D. N., Clarke, J. R., and Foster, R. T.
Rushton, J. See Goldsworthy, L. J.
Said, Mrs. See under Mustafa, Akila.
Schönberg, A., Mustafa, A., Barakat, M. Z., Latif, N., Moubasher, R., and Mustafa, Akila, 2126.
Selton, B. See Childs, A. F., and Goldsworthy, L. J.
Sharp, T. M. See Platt, B. C.
Sharpe, A. G., and Emeléus, H. J., 2135.
Simpson, J. C. E., and Wright, P. H., 2023.
Simpson, J. C. E. See also Keneford, J. R., and Morley, J. S.
Smith, L. M. See Goldsworthy, L. J.
Stern, E. S. See Cook, A. H.
Sutherland, G. B. B. M. See Brownlie, I. A.
Todd, A. R. See Bick, I. R. C., and Brownlie, I. A.
Tompsett, A. L. L. See Childs, A. F.
Ubbelohde, A. R. See Menary, J. W.
Urbański, T. See Galinowski, S.
Waley, S. G., 2008.
Walker, E. W. See Hey, D. H.
Walker, T. See Badger, G. M.
Ward, E. R. See Hodgson, H. H.
Weber, K., and Asperger, S., 2119.
Weeks, G. A. See Childs, A. F.
Weil-Malherbe, H., and Weiss, J., 2164.
Weiss, J. See Weil-Malherbe, H.
Wiggins, L. F. See Gregory, (Mrs.) H., Homer, R. F., Montgomery, R., and Overend, W. G.
Wood, J. F. See Emeléus, H. J.
Woodcock, D. See Batt, R. F.
Woolf, L. I. See Cooper, K. A., Dhar, M. L., and Hughes, E. D.
Wright, J. See King, H.
Wright, M. J. See Menary, J. W.
Wright, P. H. See Simpson, J. C. E.
Wright, S. E., 2005.

ERRATA.

VOL., 1948.

Page	Line	
1508		In Formula (IV), the "Br" should be attached to the "C" immediately below it by a vertical bond.
1596	22*	for "*2-acetoxyethyl sulphide*" read "*methyl 2-acetoxyethyl sulphide*".

* From bottom of the page.

INFORMATION FOR CANDIDATES FOR FELLOWSHIP

The Chemical Society was founded in 1841 and received a Royal Charter in 1848.

The main function of the Society is to foster original research in chemistry and to facilitate the discussion and dissemination of new knowledge in all branches of the science.

Fellowship of the Society is open to men and women of all nationalities who are interested in chemistry and wish to keep in touch with its advances. Fellows are elected by the Council.

PRIVILEGES

Fellows who pay the annual subscription of £3 10s. have the following privileges.

1. To receive a selection of the Society's publications. Publications in excess of those allowed under the Annual Subscription may be purchased at favourable rates. Details are available on application to the General Secretary.
2. To consult and borrow the books in the Library.
3. To attend meetings of the Society both in London and outside London, and to introduce two guests thereto.
4. To apply for research grants.
5. To submit original papers for publication in the *Journal*.

Fellows under the age of 25, who so wish, may pay an annual subscription of £1 15s. and enjoy all the privileges accorded to those paying the full subscription except that the choice of publications is limited.

PUBLICATIONS

(*a*) *The Journal of the Chemical Society*, which is published monthly, contains the results of investigations which cover the whole field of pure chemistry.

(*b*) *British Abstracts*.—The Society collaborates with the Society of Chemical Industry, the Physiological Society, the Biochemical Society, and other organisations in contributing to the maintenance of the Bureau of Abstracts, which issues every month abstracts of papers dealing with all branches of pure and applied chemistry, physiology and anatomy published in all parts of the world.

British Abstracts A is divided into three sections: AI, General, Physical, and Inorganic Chemistry; AII, Organic Chemistry; AIII, Physiology and Biochemistry, including Anatomy.

(*c*) *Annual Reports on the Progress of Chemistry*.—These reports, written by experts, summarise the important new advances in pure chemistry and related subjects.

(*d*) *Quarterly Reviews* are composed of articles on selected topics from the whole field of chemistry.

LIBRARY

The extensive reference and lending library of the Chemical Society contains over 47,000 volumes dealing with every aspect of chemistry and with many branches of related sciences. The library is open on Monday to Friday from 10 a.m. to 9 p.m., and on Saturdays from 10 a.m. to 5 p.m.

Books available on loan may be sent by post to Fellows residing in Great Britain or Ireland.

MEETINGS

(*a*) *In London*.—Scientific Meetings of the Society are held usually on the first and third Thursdays of each month from October to June at Burlington House, at which papers dealing with original work are read and discussed, organised discussions on subjects of current interest are arranged, and lectures by eminent British and foreign chemists are delivered.

(*b*) *Outside London*.—Scientific Meetings and lectures arranged by the Society's Local Representatives are also held outside London, and form an important part of the activities of the Society.

RESEARCH FUND

A Research Fund is available for the assistance of chemical research, and sums amounting annually to about £700 are granted for this purpose. Application for grants must be made on the appropriate form, which may be obtained from the General Secretary.

Forms of Application for Fellowship can be obtained from THE GENERAL SECRETARY, THE CHEMICAL SOCIETY, BURLINGTON HOUSE, PICCADILLY, LONDON, W.1.

NOTICES TO AUTHORS OF PAPERS

1. All Scientific Communications for the *Journal* should be addressed to " The Secretaries, The Chemical Society, Burlington House, W.1." Papers to be read before a meeting of the Society are selected by the Secretaries.

2. A paper is not normally considered for publication in the *Journal* unless at least one of the authors is a Fellow of the Society, but in exceptional circumstances the Council is prepared to consider papers submitted by non-Fellows.

3. Communications which have appeared or have been accepted for publication with essentially the same scientific content in any other Journal or freely available printed work shall not be published in the *Journal* of the Society unless this course is approved by the Council.

4. Any paper describing work done under a Government Department or similar body must be accompanied, when necessary, by a written authority approving the submission of the paper for publication in the *Journal*.

5. Authors are requested to see that their papers conform, as nearly as possible, to the normal style, conventions, and conciseness of the *Journal*.

6. Authors are solely responsible for the factual accuracy of their papers. They are particularly requested to verify references.

7. Authors are expected to be familiar with the normal rules of nomenclature, but are invited to communicate with the Editor if they are in doubt about suitable names for particular compounds or if for any special reason they wish to employ names other than those customary in the *Journal*. A convenient résumé of the principles followed in the *Journal* is given in " Modern Chemical Nomenclature ", by Dr. Clarence Smith (*J.*, 1936, 1067); reprints of this paper may be obtained by Fellows, price 2*d*. post free, on application to the General Secretary. Authors should choose their symbols from the " Report of a Joint Committee of the Chemical Society, the Faraday Society and the Physical Society on Symbols for Thermodynamical and Physico-Chemical Quantities and Conventions Relating to their Use "; copies of this publication may be obtained by Fellows, price 4*d*. post free, on application to the General Secretary.

8. Every paper should be prefaced by a short summary setting forth briefly and in simple language the objects of the investigation, the results obtained, and their bearing on chemical knowledge in general. The summary should be such as to enable any chemist to obtain a clear idea of what the investigation has achieved and should normally be from 50—250 words in length. Communications for " Notes " do not require a summary.

9. New compounds should be indicated by underlining the name at its first mention (excluding headings) both in the introduction and in the experimental section, and by giving analytical results in the form: " Found: ———. ——— requires ———." Analytical results for compounds which have previously been adequately described in the literature should be given in the form: " Found: ———. Calc. for ———: ———."

10. All papers should be submitted in typescript in double-line spacing, and on one side only of the paper. The paper used should be non-absorbent. Footnotes add considerably to the cost of printing: authors are requested, therefore, not to use them unless necessary.

11. Illustrations accompanying the papers must be carefully drawn, preferably *twice* the size of the finished block (max. width 6 inches), *in Indian ink, on smooth white Bristol board or paper* (graph paper with faint blue lines is acceptable). Any illustration which seriously exceeds four times the size of the finished block will be returned to the author for re-drawing to a smaller scale. Lettering on the drawings, whether on the margin or in the body of the drawing, must not be in ink but must be inserted *lightly, in blue pencil*. Authors may, if they wish, submit in the first place clearly drawn pencil sketches instead of the completed diagrams, which, however, must be supplied before publication. Further information can be obtained from the Editor.

12. The address to which proofs are to be sent should be written on every paper. Authors resident overseas are requested to name agents in Britain to whom may be referred matters concerning their papers, including the correction of proofs, in order that delay in publication may be avoided.

13. If any author requires more than the number of reprints (without wrappers) allowed by the Society, namely 10 plus 10 extra for each author in excess of one, or desires to receive his reprints in wrappers, and is willing to pay the extra cost thereby involved, he should place an order on the form provided at the time of returning proofs.

14. The Society reserves the right to retain all papers sent to it, and authors are therefore advised to keep copies. When papers have been accepted for publication the authors are not at liberty, save by permission of the Council, to publish them elsewhere until they have appeared in the *Journal* of the Society. Papers which are retained by the Council after being judged unsuitable for publication in the *Journal* are deposited in the Archives of the Society; this right is not usually exercised in regard to illustrations.

THE NATION'S FOOD

A SURVEY OF SCIENTIFIC DATA

Edited by A. L. BACHARACH, M.A.(Cantab), F.R.I.C. and THEODORE RENDLE, F.R.I.C.

With an Introduction by SIR JOSEPH BARCROFT, C.B.E., F.R.S.

An Authoritative Book by Eminent Specialists

Medium 8vo. xviii + 349 pages.

CONTRIBUTORS

W. B. Adam, M.A.; Mary Andross, B.Sc.; A. L. Bacharach, M.A., F.R.I.C.; L. C. Baker, M.Sc.; E. C. Bate-Smith, Ph.D.; R. G. Booth, Ph.D.; R. H. Carter; Harriette Chick, C.B.E., D.Sc.; C. L. Cutting, Ph.D.; E. H. Callow, Ph.D., F.R.I.C.; E. M. Cruickshank, D.Sc.; W. P. Ford, M.A., A.R.I.C.; N. Goldenberg, M.Sc., F.R.I.C.; R. B. Haines, D.Sc.; John Hammond, D.Sc., F.R.S.; C. R. Jones, Ph.D., F.R.I.C.; D. W. Kent-Jones, Ph.D., F.R.I.C.; S. K. Kon, D.Sc., F.R.I.C.; L. H. Lampitt, D.Sc., F.R.I.C.; J. A. Lovern, D.Sc., F.R.I.C.; A. T. R. Mattick, Ph.D.; H. C. Moir, B.Sc., F.R.I.C.; T. Moran, D.Sc.; Joseph Needham, Sc.D., F.R.S.; Mamie Olliver, M.Sc., F.R.I.C.; Magnus Pyke, Ph.D., F.R.I.C.; G. A. Reay, Ph.D.; R. N. Salaman, D.Sc., F.R.S.; J. M. Shewan, Ph.D.; H. V. Taylor, O.B.E., D.Sc.; R. S. Wimpenny, M.Sc.

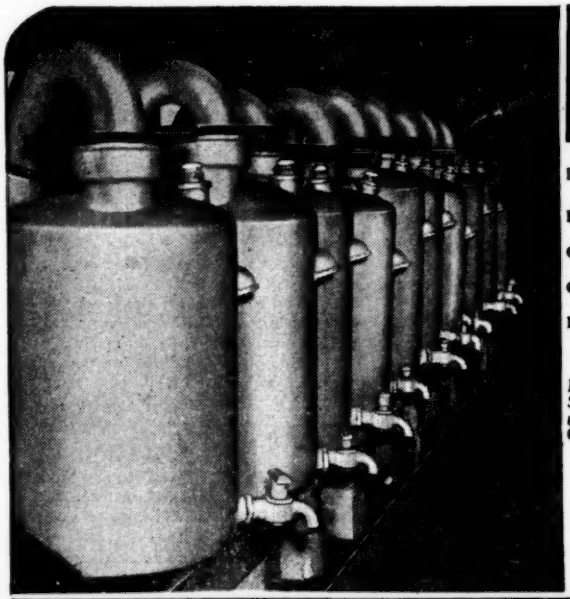
Some thirty authors have contributed to this book. Many of them are well known for their original contributions in the fields of biochemistry or food technology. They come from laboratories at academic centres, at government research institutions and at food factories. The book thus represents a piece of scientific collaboration by experts selected without any consideration other than their ability to assemble information and give it accurate expression. The authors have brought together all the knowledge at present available about the composition of the foods, and therefore the diets, of the British people. This has involved a detailed examination of seven main foods or groups of foods and the recording of innumerable data giving their chemical compositions.

The widest possible view has been taken as to the meaning of the words "chemical composition"; besides including vitamins, amino-acids and other constituents of less clear function (nucleo-tides, nitrogenous bases and so on), authors have given attention to the physical properties of the foods and also to the effect on them of cooking and processing. Based on a series of lectures given in war-time Britain, the seven parts of this book have much more than an ephemeral value.

1947

Price 18s. net

All orders for copies of this book should be sent through any bookseller to The Society of Chemical Industry, Conjoint Chemical Office, 9/10 Savile Row, London, W.1.



Standing the Acid Test!

Doulton Chemical Stoneware is outstanding in these features:

RESISTS CORROSION and all acids except hydrofluoric.
GREATER STRENGTH — the result of constant research.
CLEANLINESS — Easy to keep clean. Free from contamination.
ECONOMICAL — Initial outlay compares favourably with other materials. Maintenance and replacement costs reduced.

Photograph shows battery of Doulton Chemica Stoneware Upright Receivers, each holding 60 gallons, installed in the nitration plant of Carnegie Chemicals (Welwyn) Ltd.

DOULTON
CHEMICAL STONEWARE
For further particulars write to Dept. C.

Doulton & Co. Limited, Doulton House, Albert Embankment, London, S.E.1

Hydroxylamine hydrochloride; *p*-Nitrobenzaldehyde; Benzoin; Thiophene Quinolinic acid; Dimedone; Acrylonitrile; Nitron; Hexoestrol; Dienoestrol Stilboestrol; and Dipropionates; Adenosine-3-phosphoric acid; Calcium adenosine-5-triphosphate; α-Naphthalene-acetic acid; β-Naphthoxy-acetic acid; Juglone *N*-Brom succinimide; Diphenic acid; *cyclo*Pentanone; Boron trifluoride 48% Semicarbazide hydrochloride Adenine; Thymonucleic acid β-Indolyl-acetic acid *p*-Amino-hippuric acid Thioglycollic acid Osmium tetroxide Ethyl carbamate α : α′-Dipyridyl Amino acids Menaphthone Erythritol Adenosine Hippuric acid Thiophenol Iodoacetic acid Skatole; Ribose Bromo-acetic acid Hydrazine hydrate Erythrityl tetranitrate BP Orcinol; Ninhydrin Picrolonic acid; Raney nickel Glutaric acid; Suberic acid Acetomenaphthone; *o*-Phenanthroline HCl or hydrate; Carbachol; Carcinogenic hydrocarbons; *N*-Ethyl piperidine; Dioxan; β-Sitosterol; Cyanuric acid Indole; 2-Amino-heptane sulphate; Acetylenic compounds; Ethyl mercaptan Aluminium oxide; Dimethyl glyoxime; Nioxime; Anthrone; Biuret; Diacetyl 2 : 3 : 5-Triphenyl-tetrazolium chloride; Pimelic acid; Picolinic acid; Succinimide.

ORGANIC CHEMICALS for RESEARCH

L. LIGHT & Co. Ltd.

WRAYSBURY, near STAINES, MIDDX.

Telephone: Wraysbury 62 & 137

1949 Catalogue now available

CHEMICAL SOCIETY MEMORIAL LECTURES

VOLUME II, 1901-1913. Price 8s. 0d., postage 6d.

CONTENTS

THE RAMMELSBERG MEMORIAL LECTURE. By Sir Henry A. Miers, F.R.S. *Delivered December* 13, 1900
THE RAOULT MEMORIAL LECTURE. By J. H. Van't Hoff, F.R.S. *Delivered March* 26, 1902
THE WISLICENUS MEMORIAL LECTURE. By W. H. Perkin, Jun., F.R.S. *Delivered January* 25, 1905
THE CLEVE MEMORIAL LECTURE. By Sir Thomas Edward Thorpe, C.B., F.R.S. *Delivered June* 21, 1906
THE WOLCOTT GIBBS MEMORIAL LECTURE. By F. Wigglesworth Clarke. *Delivered June* 3, 1909
THE MENDELÉEFF MEMORIAL LECTURE. By Sir William A. Tilden, F.R.S. *Delivered October* 21, 1909
THE THOMSEN MEMORIAL LECTURE. By Sir Thomas Edward Thorpe, C.B., F.R.S. *Delivered February* 17, 1910
THE BERTHELOT MEMORIAL LECTURE. By H. B. Dixon, F.R.S. *Delivered November* 23, 1911
THE MOISSAN MEMORIAL LECTURE. By Sir William Ramsay, K.C.B., F.R.S. *Delivered February* 29, 1912
THE CANNIZARRO MEMORIAL LECTURE. By Sir William A. Tilden, F.R.S. *Delivered June* 26, 1912
THE BECQUEREL MEMORIAL LECTURE. By Sir Oliver Lodge, F.R.S. *Delivered October* 17, 1912
THE VAN'T HOFF MEMORIAL LECTURE. By James Walker, F.R.S. *Delivered May* 22, 1913
THE LADENBURG MEMORIAL LECTURE. By F. S. Kipping, F.R.S. *Delivered October* 23, 1913

Publishers: **THE CHEMICAL SOCIETY, BURLINGTON HOUSE, PICCADILLY, LONDON, W.1.**

THE SWISS CHEMICAL SOCIETY

The Swiss Chemical Society, founded in 1901, aims at encouraging the development of research in all branches of Chemistry, for which purpose it publishes a Journal of pure Chemistry, for the recording of such research.

Membership is open to individuals or Corporate bodies.

Every candidate must be proposed by two members of the Society to whom he is personally known. Forms of application can be obtained from the Secretary of Helv. chim. acta, Spitalstrasse 51, Basle, Switzerland. The entrance fee is 2 Swiss francs; the annual subscription amounts to 25 Swiss francs for members residing in Switzerland and 28 Swiss francs for members resident in foreign countries. All payments should be made to the Treasurer, Dr. M. Hartmann, Ciba Company Ltd., Basle, Switzerland.

Members receive post free :

1. Invitations to and programmes of the ordinary meetings, which are held in the Spring and Autumn alternately in different cities of Switzerland.

2. The Journal of the Society, Helvetica chimica acta (price 35 francs, plus postage), containing about 200 papers in the three national languages and occasionally in English. The Journal publishes approximately 1800–2000 pages per annum.

ANALYSTS SPECIFY

VITREOSIL (FUSED SILICA)

FILTERING AND IGNITION CRUCIBLES

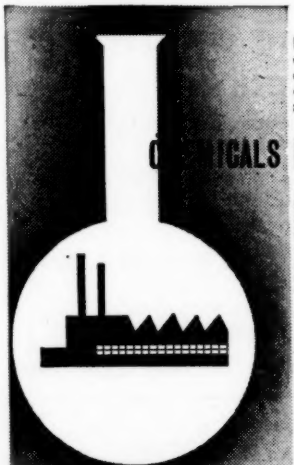
because no filter papers or asbestos mats are required, and they can filter, ignite, and weigh precipitates all in the same crucible.

In addition, four grades of porosity are available for retention of material ranging from coarse grains to fine precipitates such as Ba SO_4.

THE THERMAL SYNDICATE LTD

Head Office: WALLSEND, NORTHUMBERLAND

London Office: 12–14, Old Pye St., Westminster, S.W.1



Backed by over 100 years of experience, SPENCE chemicals are playing an increasing part in industry, and earning an ever-growing reputation for excellence and consistent quality. Chiefly concerned with the manufacture of Aluminous Compounds, SPENCE also produce Titanium Salts, Silicas and special Pharmaceutical Chemicals.

CHEMICALS FOR INDUSTRY

SPENCE chemicals include Alum, Aluminium Sulphate, Aluminium Chloride Solution, Alumina White, Activated Alumina, Calcium Carbonate, 'MULSOID' detergents, Silica, 'NEOSYL' Amorphous Silica, 85%. 'NEOSYL' Asbestos, Pharmaceutical Alumina, Sodium Aluminate, Sulphuric Acid, Titanous Chloride and Titanous Sulphate, Titanium Tetrachloride, 'TYPHOX' (Titanium phospho-oxalate), T.P.O. (Titanium potassium oxalate), and Special Pharmaceutical and Industrial Chemicals.

An abridged booklet dealing with the range of SPENCE chemicals will gladly be sent on request

PETER SPENCE & SONS LTD.

NATIONAL BUILDINGS · MANCHESTER 3

LONDON WIDNES GOOLE BRISTOL

2680x

PYREX

Registered Trade Mark

GRADUATED GLASSWARE

PYREX Brand Graduated Glassware gives you every satisfaction, inasmuch as that all division lines and numerals are etched clearly and precisely for easy reading. It also gives an assurance of safety, by the fact that the low co-efficient of expansion of $3{\cdot}2 \times 10^{-6}$ per degree C. has the effect of minimizing fracture from sudden heat or cold.

Through this latter feature, it has been possible to make the structure of PYREX Brand Graduated Glassware more robust than that of ordinary laboratory glass, thus reducing by a high percentage the cost of glassware replacements.

For everyday laboratory work PYREX Brand Glassware is Graduated to N.P.L. Class B standard, but for more meticulous analysis or intricate research work, N. P. L. Class A can be supplied at a reasonable extra cost.

PYREX

Registered Trade Mark Brand

GRADUATED GLASSWARE

made by

James A. Jobling & Co. Ltd.,

Wear Glass Works, Sunderland.

G888

THE ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND

Founded 1877 Incorporated by Royal Charter, 1885

APPOINTMENTS REGISTER.—A Register of Chemists (Fellows, Associates and Senior Registered Students) who are available for appointments, or who are seeking to improve their positions, is kept at the office of the Institute.

The facilities afforded by this Register are available (free) to Companies and Organisations requiring the services of Chemists and to Universities, Colleges and Technical Schools requiring Teachers of Chemistry and Technology.

Particulars of the Regulations and Examinations of the Institute can be obtained free on application to the Registrar,

The Royal Institute of Chemistry, 30, Russell Square, London, W.C.1

FOR LABORATORY USE

STOCKED BY ALL LABORATORY FURNISHERS IN SEALED BOXES

WHATMAN High Grade **FILTER PAPERS**

Ensure absolute accuracy in your analytical tests

Makers
W. & R. BALSTON LIMITED

Free samples on request from Sole Sales Representatives
H. REEVE ANGEL & CO., LIMITED
9 Bridewell Place, LONDON, E.C.4.

LEWIS'S BOOKS ON THE CHEMICAL AND ALLIED SCIENCES

Scientific and Technical Books :: Large Stock of Recent Editions.
Foreign Books not in stock obtained under Special Licence.

THE SECONDHAND DEPARTMENT at **140 GOWER STREET** contains a large stock of scientific and technical literature, both modern and historical; periodicals, etc. Out of print items are sought for and reported free of charge.

BOOKS BOUGHT:—Lists submitted should give author, short title, and date of publication.

H. K. LEWIS & CO. Ltd., 136 Gower Street, London, W.C.1

Telephone: EUSton 4282 (5 lines)

THE WORLD'S GREATEST BOOKSHOP

FOYLES

*** FOR BOOKS ***

New and secondhand Books on every subject

119-125 CHARING CROSS ROAD, LONDON, W.C.2

GERrard 5660 (16 lines) * Open 9-6 (inc. Sat.)

TOWER PACKINGS
OF ALL KINDS AND SIZES

SOLE SUPPLIERS
OF
LESSING CONTACT RINGS
FOR
LARGE CONTACT SURFACE
PER UNIT VOLUME

THE HYDRONYL SYNDICATE LTD.
14 Gloucester Road, London, S.W.7
Tel.: WEStern 4744 *Teleg.:* HYDRONYL, KENS, LONDON

GREEN'S Lens Tissue No. 105
★ *for absolutely clean lenses*
In booklets and sheets and it is now obtainable from all dealers. We can deliver to dealers by return. Ask for List OG/T.
J. BARCHAM GREEN LIMITED
MAIDSTONE **ENGLAND**

THE CHEMICAL SOCIETY
Annual Reports on the Progress of Chemistry
Copies of the forty-fourth volume of this annual series are still available and may be obtained from the publishers. The next volume, summarising the advances that have been made in pure chemistry and related subjects up to the end of 1948 will be published early in 1949. Since the inception of Annual Reports in 1904 they have provided chemists the world over with an essential service. The price of this valuable publication to non-Fellows is £1 net.
Published by **THE CHEMICAL SOCIETY**
BURLINGTON HOUSE, PICCADILLY, LONDON, W.1

RESPIRATORS
for work in Poisonous, Noxious and Irritant Fumes
OXYGEN BREATHING APPARATUS
also compressed air types
SMOKE HELMETS
OXYGEN RESUSCITATION APPARATUS
for asphyxia, electric shock, etc.
ACID AND WATERPROOF CLOTHING, GOGGLES, GLOVES, FUME MASKS, ETC.
SIEBE, GORMAN & CO. LTD. LONDON
EVERYTHING FOR SAFETY EVERYWHERE
TOLWORTH, SURBITON, SURREY

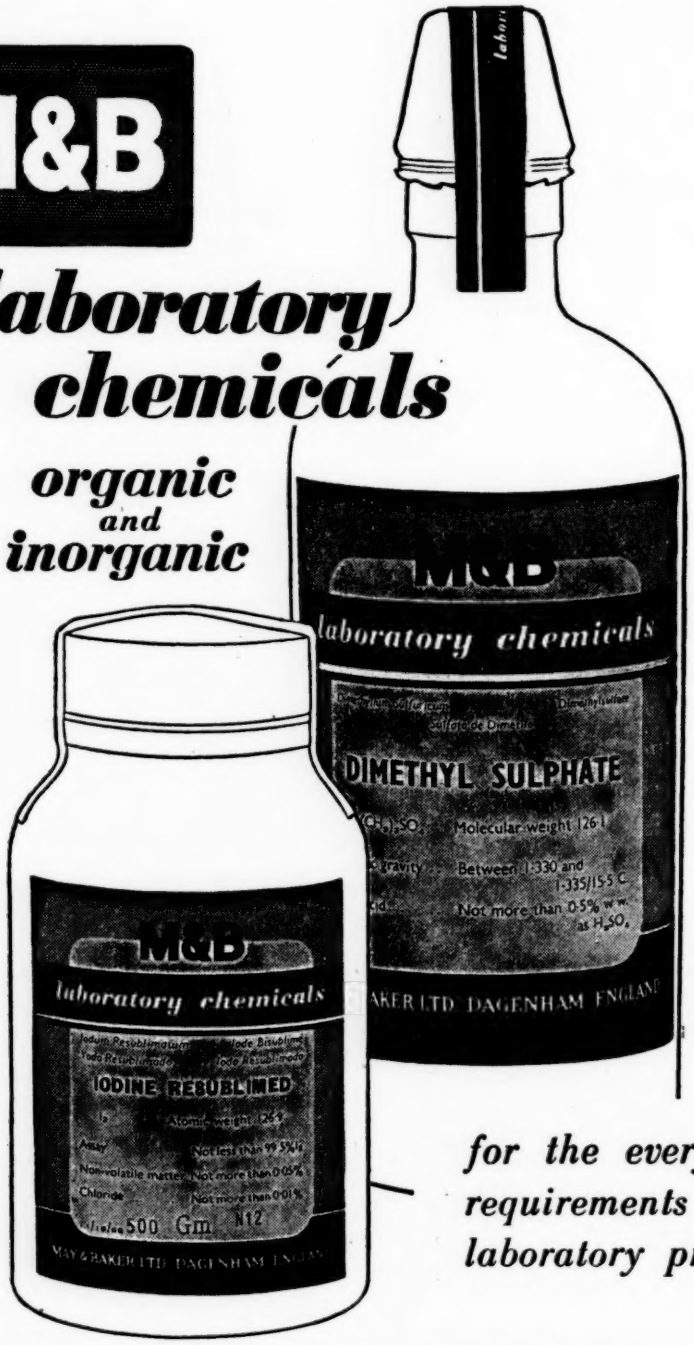
pH SIMPLIFIED MEASUREMENT
Industrial Chemists and research workers should obtain particulars of these useful test papers made by JOHNSONS OF HENDON. There are five books in the series. UNIVERSAL is a single paper covering, completely, the range from 1 to 10 and enabling *pH* values to be checked to within 0.5*pH*. For more exacting work COMPARATOR test papers, in four books, enable the *pH* value of any solution to be ascertained to within 0.3*pH*.
Descriptive leaflet sent free on application
JOHNSONS OF HENDON LTD
LONDON, N.W.4. ESTAB. 1743

C.H. 3057a

M&B

laboratory chemicals

organic and inorganic



for the everyday requirements of laboratory practice

A brochure containing full details of specifications will gladly be sent on request.

MAY & BAKER LTD

ILFord 3060. Ext. 219 **DAGENHAM**

He says about the stereochemical researches based on optical activity, " Although the researches have not led to any comprehensive generalization, they have revealed a number of interesting regularities, which form in some measure a compensation for the enormous amount of labour which has been bestowed on the subject, which is admittedly of great complexity."

Optical Activity in Homologous Series.—The esters of glyceric and acetylglyceric acid, ranging from methyl to octyl, were prepared from lævorotatory glyceric acid, obtained by the fermentation method (*J.*, 1893, **63**, 511, 1410, 1419; 1894, **65**, 750, 760; 1897, **71**, 253). The curves for the rotatory power of the glycerides and acetylglycerates showed a flat maximum in the position of the 4th to 6th members of the homologous series, and they ran parallel to one another. The positions of the maxima were approximately what would be expected from the Crum Brown–Guye hypothesis, but the breakdown of this hypothesis was very clearly evident in the case of the methyl and ethyl diacetylglycerates (*J.*, 1894, **65**, 750). For these substances, two groups around the asymmetric carbon atom are of equal mass and therefore the product of asymmetry is zero, whereas both are powerfully optically active. He concludes that since the maximum occurs at the same place in the glycerates and acetylglycerates, it is very likely that the position of maximum rotation is determined by some property of the hydrocarbon chain rather than by the product of asymmetry.

Frankland studied two further homologous series in some detail, the dibenzoylglycerates (*J.*, 1896, **69**, 104) and the dimethoxypropionates (*J.*, 1905, **87**, 864). In the former, the maximum occurred very early in the series at the second member, and in the latter at the seventh member. In his presidential address to the Chemical Society in 1912 he summarises his own work and that of Tschugaeff, Guye and Chavanne, Pickard, Kenyon, and others on the optical rotatory power of homologous systems. " In some series there is a progressive change in the molecular rotation until a maximum is reached and this is followed by a much less marked decline in the rotation, which tends towards a limiting value. In other series, the rotation progressively changes, a limiting value being reached without the appearance of any definite maximum or minimum. In either case the maximum or limiting value is generally reached at a surprisingly early term in the series." After a very careful critical exmination of all the experimental results (*J.*, 1899, **75**, 347), he came to the conclusion that the position of the maximum could not be linked with association phenomena, nor could it be accounted for by the changes in masses of the groups around the asymmetric carbon chain. He made the suggestion that " according to the commonly accepted view of stereochemistry, a continuous chain of five carbon atoms will all but return on itself, and beyond this, further addition to the chain will lead to such interference as must necessitate a readjustment of the exact position occupied by the carbon atoms in the shorter chain. It is surely highly probable that the stereochemical change should be betrayed by some irregularity in the rotation manifestations, for example, by the exhibition of a rotation maximum."

Position Isomerism in Aromatic Compounds on Molecular Rotation.—The introduction of a cyclic group such as benzoyl, toluoyl, pyromucyl, or phenacetyl in near proximity to an asymmetric carbon atom always produced a marked change in the optical rotatory power. The deviation was sensitive to small changes in the constitution of the cyclic group and thus afforded a means of studying the stereochemical changes occurring on substitution. Frankland suggested (*J.*, 1896, **69**, 1309, 1583; 1898, **73**, 307; 1901, **79**, 266) that for reasons based on the relative position of the centre of gravity of the aromatic nucleus, the effect on the optical rotatory power of the *o*-, *m*-, and *p*-substituted benzoyl groups should be in the order ortho<phenyl<meta<para. This was found to be generally true, although some anomalous effects due to variable temperature coefficients of the rotatory power or possibly to association to double molecules were responsible for minor irregularities. It was almost invariably found that the *o*-toluoyl group had a rotatory effect of a different order from those of the phenyl and *m*- and *p*-toluoyl groups, which were always close together, but the relative order of the last three groups was in a few cases not in line with the above sequence. The validity of the rule was confirmed by Cohen (*J.*, 1910, **97**, 1732) for a large number of substituted methyl benzoates, and in all of the nine cases studied, the rule, ortho<phenyl<meta was found to hold.

A number of series were found for which the reverse order held, the dextrorotatory effect of the substitutions being in the order, para<phenyl<meta<ortho for the methyl and ethyl toluoylmalates (*J.*, 1899, **75**, 337) and ditoluoylglycerates (*ibid*, p. 493).

Series in which the methyl group was replaced by the nitro-group and the halogens followed. The esters of the di- *o*-, *m*-, and *p*-nitrobenzoyltartrates were compared with the toluoyl derivative (*J.*, 1904, **85**, 1571). The order for the methyl esters was para<meta<ortho, and for the ethyl esters the same relationship held at high temperatures, but the ethyl di-*o*-nitrobenzoyl-

tartrate had an anomalously high temperature coefficient, which led to departures from the rule at the lower temperatures. In the final paper on the series on benzoyltartrates (*J.*, 1912, **101**, 2470), the chloro-, bromo-, and iodo-derivatives gave very convincing support for Frankland's rule, supplementing it by some very interesting conclusions which showed the sensitiveness of this method of approach to stereochemistry. The halogens exert an influence on the rotatory power which is of the same kind as that of the methyl group in the toluoyl radical, but in a greater degree. The order para<meta<ortho is maintained, but the rotatory effect increases with the atomic weight of the halogen.

The same general relationships were found when the cyclic group was attached to the amido-groups of tartramide (*J.*, 1903, **83**, 1349). The order of exaltation was para>meta>anilide>ortho, the substitution behaving similarly to that of the same aromatic groups into the hydroxyl groups of tartaric acid. A close parallelism was found between the effects of the acetyl, phenacetyl, benzoyl, and toluoyl groups replacing the hydrogen atom of the hydroxyl groups of the optically active hydroxy-acids and those due to ethylamine, benzylamine, aniline, and toluidine replacing the hydroxyl of the carboxyl group. Although the halogens replacing methyl in the aromatic groups (*J.*, 1910, **97**, 154) increase the exaltation they, however, appear to have an effect by virtue of their electronegative character, which Frankland suggests is possibly due to the intramolecular attraction forces between the negative group and the hydrogen of the tartaric nucleus, which changes the asymmetry.

Rotatory Effects of Specific Groups.—A very large amount of data was accumulated by Frankland and his pupils on the specific effects of particular groups, notably on the effects of double bonds, cyclic groups, and nitro-groups as compared with methyl groups, halogen groups, etc. The work is difficult to summarise, since the effect of the substitution depended on the asymmetry of the molecule as a whole, and also on the solvent used. Certain regularities were, however, found, some of which are summarised in his presidential address in 1912 (*J.*, 1912, **101**, 654).

Unsaturation. "There is a general consensus of opinion that of two similar groupings, *the one saturated and the other unsaturated, the latter will have the greater rotatory effect.* It would, however, in my opinion, be more correct to say that the presence of unsaturation leads to an *irregularity in the rotatory effect, and not necessarily to an increase in rotation.*" The relations are not so simple and harmonious as at first supposed; in some cases, the double linking has a smaller effect on the rotatory power than the saturated grouping. Conjugated double bonds, however, exercise a very powerful exaltation, as pointed out by Rupe and Hilditch.

In the case of some *n*-propyl and allyl derivatives of menthol (*J.*, 1911, **99**, 2325) the differences were small, and this is ascribed to the great distance of the double bond from the asymmetric carbon atom. The constitutional change is made at such a great distance from the asymmetric carbon atom that it has little effect on the rotation.

It was shown that, in the substitution of both tartramide (*J.*, 1906, **89**, 1852) and malamide (*ibid.*, p. 1899) by *n*-propyl and allyl alcohol respectively, the *n*-propyl derivative had the higher rotation, which is contrary to the accepted rule. Here again the active group is 3 or 4 carbon atoms removed from the asymmetric atom. The behaviour in these substances is also very much affected by the solvent in which the rotation is measured.

However, in certain derivatives of tartramide, $NHR{\cdot}CO{\cdot}[CH{\cdot}OH]_2{\cdot}CO{\cdot}NHR$, in which R is varied, the influence of unsaturation is brought out very clearly (*J.*, 1903, **83**, 1349).

	$M_D^{20°}$.		$M_D^{20°}$.
—C(—)—$CO{\cdot}NH_2$	+ 158°	—C(—)—$CO{\cdot}NH{\cdot}N{:}CH{\cdot}C_6H_5$	+ 554°
—C(—)—$CO{\cdot}NH{\cdot}NH_2$	+ 170°	—C(—)—$CO{\cdot}NH{\cdot}N{:}CH{\cdot}C_4H_3O$	+ 736°

Cyclic groups. Frankland investigated the changes in rotatory power due to the introduction of conjugated and saturated cyclic groups into the optically active molecule. The rotation was not appreciably affected by saturated rings, but with conjugated rings there was a marked exaltation when they were introduced into tartrates and tartramides (*J.*, 1896, **69**, 1309, 1583; 1901, **79**, 511; 1903, **83**, 1342, 1349; 1906, **89**, 1852). The furan ring was similar to benzene in giving a considerable exaltation of the rotation, and the tetrahydrobenzene ring in *ac*-tetrahydro-β-naphthyl groups, being a saturated ring, exerted a very small rotatory effect.

The α-naphthyl group was found to resemble the *o*-toluoyl group and the β-naphthyl group the *p*-toluoyl group in their general effects. The effect of isomerism in the cyclic group has been dealt with on page 2003.

Nitro-groups. Frankland devoted much attention to the rotatory influence of the nitro-group relative to that of the methyl group. The dinitrotartaric acids and the methyl esters of mononitro- and dinitro-tartaric acids were investigated (*J.*, 1903, **83**, 154, 168). Also, the diethyl monobenzoyl- and mono-*p*-toluoyl-tartrates were nitrated. From these experiments and those quoted earlier, it is concluded that NO_2 has a higher rotatory effect than CH_3 and $O{\cdot}CH_3$ when attached to a ring, but when present as $O{\cdot}NO_2$ it has a less effect than $O{\cdot}CH_3$. These differences he ascribes to modifications in the chemical constitution of NO_2 when attached directly to carbon or through oxygen. The summary of a very complex situation as regards the relative effects of NO_2 and CH_3 groups is given by Frankland in the paper in 1903 (p. 168).

In the years preceding the first world war, Frankland was extending his range of interests in the stereochemical field. This is shown by his two presidential addresses to the Chemical Society in 1912 and 1913. He commenced researches on the Walden inversion (*J.*, 1914, **105**, 456, 1101) and on rotation dispersion (*J.*, 1919, **115**, 636). With the onset of the war his activities were entirely absorbed in Government work, and, since he retired immediately after the war, these lines were not further pursued by him.

W. E. GARNER.

---

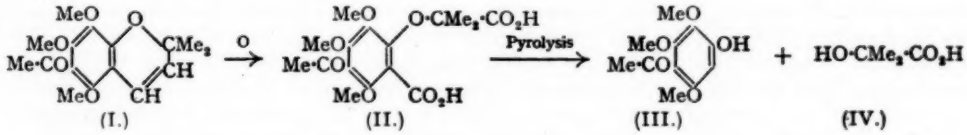
405. *The Constitution of Evodione.*

By S. E. WRIGHT.

Evodione, a colourless crystalline ketone isolated from the volatile oil of *Evodia Elleryana* has been further investigated. Degradation experiments here recorded indicate it to be 5 : 7 : 8-trimethoxy-6-acetyl-2 : 2-dimethyl-1 : 2-benzpyran. Ultra-violet absorption spectra data support the evidence.

PREVIOUS work on evodione has shown that its molecular formula is $C_{16}H_{20}O_5$, and that one ketonic and three methoxyl groups are present (Jones and Wright, *University of Queensland Chem. Papers*, 1946, No. 27). When evodione is subjected to catalytic hydrogenation, a *dihydro*-derivative $C_{16}H_{20}O_5$ is obtained, characterised by its *semicarbazone*, 2 : 4-*dinitrophenylhydrazone*, and *benzylidene* derivative. Oxidation with permanganate in cold acetone, gives a dibasic *acid*, $C_{16}H_{22}O_9$. Since this acid is formed without loss of carbon atoms it appears that a ring structure has been ruptured, most probably at the double bond revealed by hydrogenation, for the dihydro-derivative is not attacked by permanganate in acetone. When this dibasic acid is heated just above its melting point, decomposition occurs to give carbon dioxide, traces of acetic acid, a white crystalline sublimate identified as α-hydroxy*iso*butyric acid, and a glassy amorphous residue. This solid residue on extraction with sodium carbonate yields a liquid phenol which on methylation is converted into 2 : 3 : 4 : 6-tetramethoxyacetophenone, identified by comparison of its 2 : 4-*dinitrophenylhydrazone* with that of an authentic sample prepared by synthesis. The solubility of this phenol in sodium carbonate indicates that the free phenolic group is in the *p*-position to the carbonyl. After removal of the carbonate-soluble material, the residue on extraction with sodium hydroxide solution gives a second liquid phenol. This phenol on methylation and subsequent treatment with acetyl chloride in the presence of aluminium chloride is converted into 2 : 3 : 4 : 6-tetramethoxyacetophenone.

These reactions are explained satisfactorily if evodione is regarded as 5 : 7 : 8-trimethoxy-6-acetyl-2 : 2-dimethyl-1 : 2-benzpyran (I), oxidation yielding the dibasic acid (II) which on



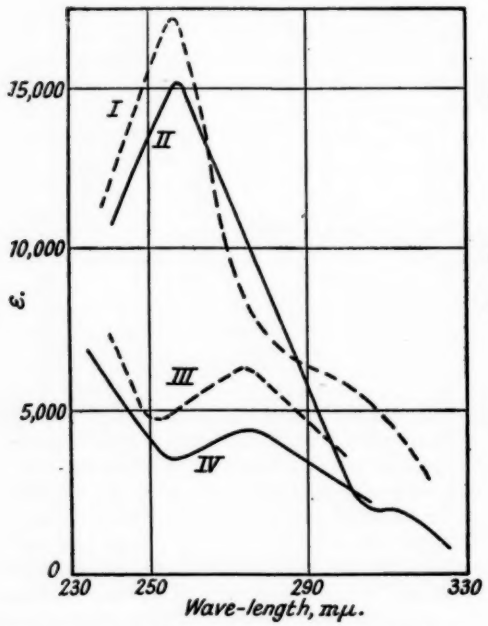
(I.) (II.) (III.) (IV.)

pyrolysis gives 4-hydroxy-2 : 3 : 6-trimethoxyacetophenone (III) and α-hydroxy*iso*butyric acid (IV). The second phenol obtained after pyrolysis is presumably 2 : 3 : 5-trimethoxyphenol, being derived most probably from (III) by deacetylation.

A qualitative test for the 2 : 2-dimethylbenzpyran nucleus has been developed (Bell, Robertson, and Subramanian, *J.*, 1936, 627), and depends upon the formation of acetone when the material is hydrolysed by refluxing with concentrated aqueous or alcoholic potassium hydroxide. Evodione, however, resists hydrolysis with either aqueous or alcoholic potassium hydroxide and is recovered unchanged after refluxing with boiling 25% alcoholic potassium hydroxide for 8 hours. Attempts to hydrolyse it with 33% alcoholic potassium hydroxide at 15 lbs. pressure for 2 hours also failed.

The decomposition of the dibasic acid (II) to give α-hydroxy*iso*butyric acid resembles that undergone by nicouic acid and tephrosindicarboxylic acid (Clark, *J. Amer. Chem. Soc.*, 1932, **54**, 3000), and supports the presence of the *gem*-dimethylbenzpyran ring in evodione. The behaviour of evodione on oxidation with acetone–permanganate is similar to that of the methyl ether of

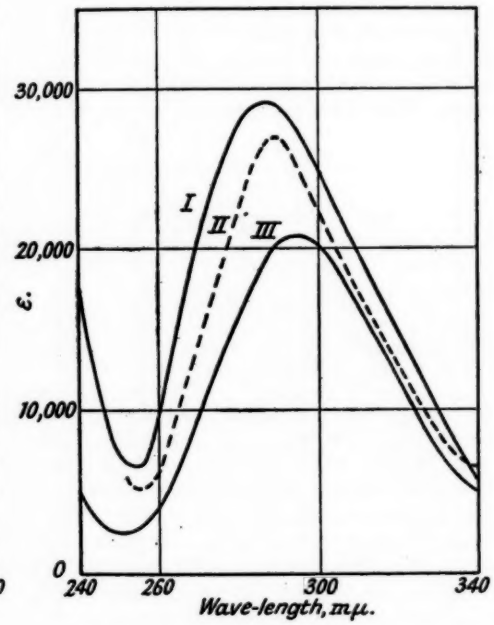
FIG. 1.



(I) *Evodionol methyl ether* (5 : 7-*dimethoxy*-6-*acetyl*-2 : 2-*dimethyl*-1 : 2-*benzpyran*).*
(II) *Evodione.*
(III) *Dihydroevodionol methyl ether* (5 : 7-*dimethoxy*-6-*acetyl*-2 : 2-*dimethylchroman*).*
(IV) *Dihydroevodione.*

* Lahey, *loc. cit.*

FIG. 2.



(I) *Benzylidene-evodione.*
(II) *Benzylidene-evodionol methyl ether.**
(III) *Benzylidenedihydroevodione.*

* Lahey, *loc. cit.*

evodionol, a phenolic ketone isolated from the volatile oil of *Evodia littoralis* and shown to be 7-hydroxy-5-methoxy-6-acetyl-2 : 2-dimethyl-1 : 2-benzpyran (Lahey, *Univ. Queensland Chem. Papers*, 1942, No. 20); this gave a dibasic acid similar to (II) but lacking a methoxyl group in the position adjacent to the side chain. When this acid was esterified with methyl alcohol in the presence of sulphuric acid, decarboxylation occurred with loss of the nuclear carboxyl group. When the dibasic acid (II) obtained from evodione is esterified with methyl alcohol and sulphuric acid no decarboxylation occurs but a *monomethyl* ester, $C_{17}H_{22}O_9,H_2O$, is obtained. Complete esterification is accomplished by using diazomethane, giving a *dimethyl* ester, $C_{18}H_{24}O_9$. It would appear that the extra methoxyl group present in the dibasic acid from evodione stabilises the nuclear carboxyl group, but steric effects prevent it from being esterified unless diazomethane is used.

Further evidence of the close relationship between evodionol and evodione was obtained by a comparison of the ultra-violet absorption spectra of closely related derivatives of each compound (Figs. 1 and 2).

Absorption data for solutions in alcohol.

	λ max., mμ.	ε max.	λ min., mμ.	ε min.
Evodione	257	15,500	—	—
	~310	2,100		
Dihydroevodione	272	4,690	254	3200
Benzylidene-evodione	288	29,000	255	6100
Benzylidenedihydroevodione	296	21,000	251	2100

Experimental.

Melting points are uncorrected.

Dihydroevodione.—Evodione (1·46 g.) was hydrogenated in alcohol at 2 atm. pressure using Adams's platinum oxide catalyst (absorbed 116 c.c., N.T.P.); a colourless *product* was obtained which crystallised from light petroleum in needles, m. p. 63° (Found: C, 65·5; H, 7·5; OMe, 31·8. $C_{16}H_{22}O_8$ requires C, 65·3; H, 7·54; 3OMe, 32·3%).

Dihydroevodione 2 : 4-*dinitrophenylhydrazone*, crystallised from alcohol in yellow needles, m. p. 162° (Found: N, 11·9. $C_{22}H_{26}O_8N_4$ requires N, 11·8%).

Dihydroevodione semicarbazone. Dihydroevodione (0·2 g.), dissolved in alcohol (2 c.c.) and pyridine (1 c.c.), was treated with semicarbazide hydrochloride (0·2 g.) dissolved in hot water (5 c.c.). The solution was evaporated on a water-bath to dryness, and the solid *product* recrystallised from dilute alcohol; m. p. 178—179° (Found: N, 12·1. $C_{17}H_{25}O_8N_3$ requires N, 11·96%).

Benzylidenedihydroevodione. Dihydroevodione (0·2 g.) was dissolved in alcohol (10 c.c.) and treated with benzaldehyde (0·2 g.) and 4% sodium hydroxide solution (8 c.c.). The mixture was shaken for 1 hour and then left overnight. Pale yellow plates separated which were recrystallised from alcohol; the *compound* had m. p. 103° (Found: C, 72·5; H, 7·0. $C_{23}H_{26}O_8$ requires C, 72·23; H, 6·85%).

Oxidation of Evodione.—Evodione (5 g.) dissolved in dry acetone (200 c.c.) was treated with potassium permanganate at room temperature with mechanical stirring until no more permanganate was reduced (12 g. used in approximately 12 hours). Water was added and the excess of permanganate reduced with a little sodium sulphite. The sludge of manganese dioxide was filtered off and washed with hot water. The filtrate and washings were combined and evaporated under reduced pressure to small volume. The solution was then acidified and extracted thrice with ether. When the ether was removed a colourless crystalline *acid* (II) was obtained and recrystallised from ether or water. It melted at 178° (decomp.). Yield 3·75 g. (Found: C, 54·0; H, 5·7; OMe, 26·4; equiv. by titration, 180; equiv. by silver salt, 179. $C_{16}H_{20}O_9$ requires C, 53·93; H, 5·6; OMe, 26·1%; equiv., 178, dibasic).

Esterification of the Dibasic Acid.—(a) *With methyl alcohol–sulphuric acid.* The dibasic acid (II) (0·6 g.) was dissolved in methyl alcohol (30 c.c.) and sulphuric acid (1 g.), and the solution refluxed for 8 hours, cooled, diluted with water, and extracted with ether. The ether layer was extracted with sodium carbonate solution, which on acidification and extraction with ether gave a crystalline acid. The acid crystallised from ether–light petroleum in needles, m. p. 95°. Yield 0·4 g. (Found; C, 52·4; H, 6·2; equiv. by titration, 383. $C_{17}H_{22}O_9,H_2O$ requires C, 52·5; H, 6·18%; equiv., 388, monobasic). 0·0776 G. required 0·8 c.c. of N/2-sodium hydroxide for saponification, and the recovered acid recrystallised from ether had m. p. 178°, mixed m. p. with original dibasic acid 178°. When heated in a vacuum at 110° for 4 hours in an Abderhalden drier (concentrated sulphuric acid), 0·0288 g. of the *monomethyl* ester lost 0·013 g. of water (calc. for loss of one mol. of water, 0·0134 g.) The resulting anhydrous *acid* was a viscous liquid which would not crystallise (Found: C, 54·6; H, 6·0. $C_{17}H_{22}O_9$ requires C, 55·1; H, 5·99%).

(b) *With diazomethane.* The dibasic acid (II) (0·5 g.) was left overnight with excess of diazomethane in ether. The excess of diazomethane was decomposed with acetic acid, and the ether solution washed with sodium carbonate. When the ether was removed an ester was isolated and recrystallised from ether–light petroleum; m. p. 77·5°. Yield 0·5 g. (Found: C, 56·3; H, 6·3. $C_{18}H_{24}O_9$ requires C, 56·2; H, 6·29%). 0·6 G. of the *dimethyl* ester required 3·1 c.c. of N/2-sodium hydroxide for saponification, and the recovered acid had m. p. 178°, mixed m. p. with original dibasic acid, 178°.

Pyrolysis of the Dibasic Acid.—The dibasic acid (II) (2 g.) was heated in a wide-mouthed test-tube connected by a delivery tube through a liquid-air trap to a vacuum pump. The temperature was maintained just above the m. p. of the acid (180—190°) until no more decomposition was noted. During the heating a sublimate of colourless crystals formed in the delivery tube. This solid was acidic and hygroscopic, had m. p. 78—79°, and gave no melting point depression when mixed with an authentic sample of α-hydroxy*iso*butyric acid. Traces of acetic acid were collected in the liquid-air trap and identified by qualitative tests. In another experiment, the acid (0·2 g.) was sealed in a tube under high vacuum and heated to 180° until no more gas was evolved. The tube was then connected to a high-vacuum system and the gases distilled off, water vapour being collected in a trap at − 40° and a sublimate of carbon dioxide in the liquid-air trap.

The solid residue remaining after pyrolysis was dissolved in ether and extracted with sodium carbonate and then with sodium hydroxide solution. On acidification, the sodium carbonate solution yielded a dark liquid (0·4 g. from 2 g. of acid) which gave a red-brown colour with ferric chloride. This liquid did not crystallise, and was methylated by refluxing with methyl sulphate and anhydrous potassium carbonate in dry acetone. The resulting methylated product gave a 2 : 4-*dinitrophenylhydrazone*, crystallising from alcohol in orange needles, m. p. 168° (Found: N, 13·0. $C_{18}H_{20}O_8N_4$ requires N 13·3%).

A carbonate-soluble phenol was also obtained when the dibasic acid (0·5 g.) was refluxed with 20 c.c. of quinoline and 1 g. of copper bronze for ½ hour, and when methylated gave the same 2 : 4-dinitrophenylhydrazone, m. p. 168°. A sample of 1 : 2 : 3 : 5-tetramethoxybenzene was prepared by synthesis from 2 : 6-dimethoxybenzoquinone (Chapman, Perkin, and Robinson, *J.*, 1927, 3015) and converted into 2 : 3 : 4 : 6-tetramethoxyacetophenone by reaction with aluminium chloride in carbon disulphide solution

(Bargelli and Bini, *Atti R. Accad. Lincei*, 1920, **19**, 595). The 2 : 4-dinitrophenylhydrazone of this compound melted at 168° and showed no depression with the above 2 : 4-dinitrophenylhydrazone.

When the sodium hydroxide solution was acidified, a liquid phenol (0·1 g. from 2 g. of acid) was obtained which gave a purplish-brown colour with ferric chloride solution. The liquid was methylated with diazomethane in ether, and the product distilled in a vacuum. The distillate (0·1 g.) proved difficult to crystallise and was therefore dissolved in acetyl chloride (0·2 c.c.), treated with aluminium chloride (1 g.), and cooled in ice–water. After ½ hour the product became semi-solid, and ice-cold water was added. The liquid was then extracted with ether, and the ether solution washed with dilute sodium hydroxide. The ether was removed, and the product distilled in a vacuum and treated with 2 : 4-dinitrophenylhydrazine sulphate in alcohol to give a 2 : 4-dinitrophenylhydrazone, m. p. 168° after recrystallisation from alcohol. This gave no depression when mixed with the 2 : 4-dinitrophenylhydrazone of 2 : 3 : 4 : 6-tetramethoxyacetophenone.

The author wishes to thank Professor T. T. H. Jones for his interest in this work, and the Commonwealth Government Research Fund for a grant.

UNIVERSITY OF QUEENSLAND, AND PHARMACY COLLEGE,
WELLINGTON, NEW ZEALAND. [*Received, December 16th*, 1947.]

---

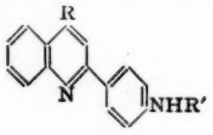
406. *Polyquinolyls.*

By S. G. WALEY.

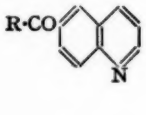
A stepwise synthesis of 2 : 6′-polyquinolyls has been effected. 2-(*p*-Aminophenyl)-quinoline (I; R = R′ = H) has been condensed with β-6-quinolylacraldehyde (V) to give 2 : 6′-triquinolyl (VI), and with *p*-nitrocinnamaldehyde to give 2-[4′-(*p*-nitrocinnamylidene)-aminophenyl]quinoline (VII), or, under more vigorous conditions, 2′-(*p*-nitrophenyl)-2 : 6′-diquinolyl (IX; R = NO_2). Reduction of the latter gave 2′-(*p*-aminophenyl)-2 : 6′-diquinolyl (IX; R = NH_2) which reacted with the aldehyde (V) to give 2 : 6′-tetraquinolyl (X). 2 : 6′-Diquinolyl-4-carboxylic acid (III; R = CO_2H) has been prepared from 6-acetylquinoline (II; R = Me) and isatin; decarboxylation gave 2 : 6′-diquinolyl (III; R = H).

THERE are several examples known of a series of short-chain molecules which are rigid in the sense that rotation does not alter the length. Thus, the polyphenyls form such a series (Busch and Weber, *J. pr. Chem.*, 1936, **146**, 1; Bowden, *J.*, 1931, 1111; Müller and Topel, *Ber.*, 1939, **72**, 290; Gillam and Hey, *J.*, 1939, 1170). This series, however, cannot be ascended by stepwise synthesis. The 2 : 6′-polyquinolyl series has now been investigated (the convenient name polyquinolyl has been retained here). The quinoline syntheses used were the Döbner (*Annalen*, 1888, **249**, 98), the Pfitzinger (*J. pr. Chem.*, 1886, **33**, 100), and the Döbner–v. Miller (*Ber.*, 1883, **16**, 1664).

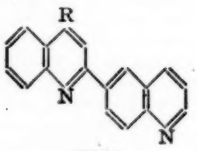
p-Acetamidobenzaldehyde (Beard and Hodgson, *J.*, 1927, 20) was condensed with aniline and pyruvic acid, according to the method of Döbner, to give 2-(p-*acetamidophenyl*)*quinoline*-4-*carboxylic acid* (I; R = CO_2H, R′ = COMe), also prepared by acetylation of the amine (I; R = R′ = H). This amine was prepared by John (*J. pr. Chem.*, 1934, **139**, 17) from isatin and *p*-aminoacetophenone; the latter could conveniently be replaced by the *p*-acetamidoacetophenone obtained from acetanilide (Kunckell, *Ber.*, 1900, **33**, 2641). When, however, *p*-acetamidobenzaldehyde was condensed with 2-(*p*-aminophenyl)quinoline (I; R = R′ = H) and pyruvic acid no pure product could be isolated.



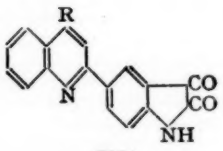
(I.)



(II.)



(III.)

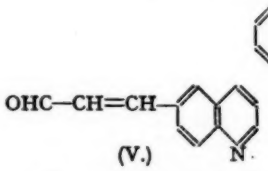


(IV.)

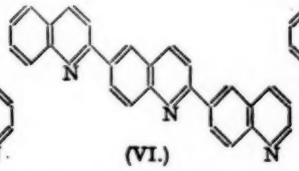
The early syntheses of quinoline-6-carboxylic acid (II; R = OH) (Skraup and Brunner, *Monatsh.*, 1881, **2**, 518; Georgievics, *ibid.*, 1891, **12**, 306) were not found satisfactory, but the modified Skraup synthesis of Cohn (*J. Amer. Chem. Soc.*, 1930, **52**, 3685) proceeded smoothly when applied to *p*-aminobenzoic acid. Direct esterification of the crude acid gave a good overall yield of ethyl quinoline-6-carboxylate (II; R = OEt), and this method seems more convenient than that described recently by Seibert, Norton, Benson, and Bergstrom (*ibid.*, 1946, **68**, 2721). Condensation of ethyl quinoline-6-carboxylate with ethyl acetate in the presence of sodium ethoxide gave 6-*acetylquinoline* (II; R = Me), which underwent the Pfitzinger condensation with isatin to give 2 : 6′-*diquinolyl*-4-*carboxylic acid* (III; R = CO_2H)

in good yield. Decarboxylation in the presence of copper carbonate readily gave 2 : 6′-diquinolyl (III; R = H), which had previously been obtained from 2-(*p*-aminophenyl)quinoline (Weidel, *Monatsh.*, 1887, **8**, 140). Attempts to prepare higher polyquinolyls by the Pfitzinger synthesis were unsuccessful, since the quinolylisatins (IV) could not be prepared. Aminophenylquinolinecarboxylic acid (I; R = CO_2H, R′ = H) reacted with chloral and hydroxylamine to give 2-(p-*oximinoacetamidophenyl*)*quinoline*-4-*carboxylic acid* (I; R = CO_2H, R′ = $CO{\cdot}CH{:}NOH$), but the isatin (IV; R = CO_2H) could not be isolated after treatment with sulphuric acid (cf. Sandmeyer, *Helv. Chim. Acta*, 1919, **2**, 234). No pure products could be isolated from the condensation of ethyl mesoxalate with either aminophenylquinoline (I; R = R′ = H) or the acid (I; R = CO_2H, R′ = H).

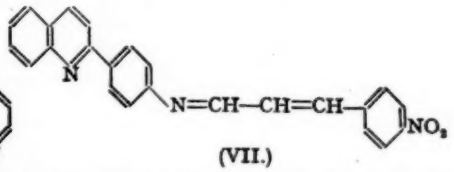
In view of the apparent difficulty in causing cyclisation of derivatives of 2-(*p*-aminophenyl)-quinoline, the quinoline synthesis of Döbner–v. Miller was investigated, since although the yields are usually low this synthesis very rarely fails. Quinoline-6-aldehyde (Rodinov and Berkengeim, *J. Gen. Chem. Russia*, 1944, **14**, 330) was condensed with acetaldehyde in an alkaline benzene–water emulsion to give β-6-quinolylacraldehyde (V). This aldehyde was heated with aminophenylquinoline (I; R = R′ = H) and hydrochloric acid to give a low yield of the desired 2 : 6′-*triquinolyl* (VI), a high-melting solid which could be sublimed in a vacuum.



(V.)

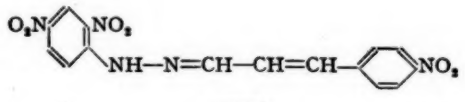


(VI.)

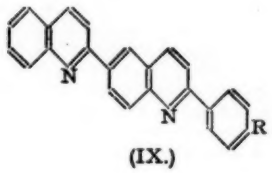


(VII.)

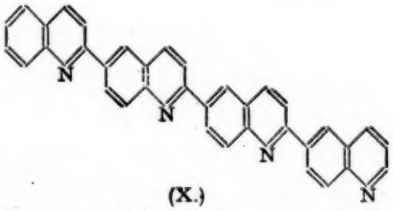
p-Nitrocinnamaldehyde was prepared from *p*-nitrobenzaldehyde (Fecht, *Ber.*, 1907, **40** 3898); details of this preparation are given in the Experimental section because the original description is brief and the conditions were found to be rather critical. When *p*-nitrocinnamaldehyde was heated with the amine (I; R = R′ = H) and hydrochloric acid at 140°, the sole product isolated was 2-[4′-(p-*nitrocinnamylidene*)*aminophenyl*]*quinoline* (VII). This structure was confirmed by fission with dinitrophenylhydrazine in sulphuric acid to the *dinitrophenylhydrazone* of *p*-nitrocinnamaldehyde (VIII), and by the alternative preparation of (VII) from *p*-nitrocinnamaldehyde and the amine (I; R = R′ = H) in ethanol solution. The isolation of the anil (VII) under the conditions used in the Döbner–v. Miller reaction suggests that such anils may be intermediates in the formation of quinolines (cf. Manske, *Chem. Reviews*, 1942, **30**, 113), and also shows how stable such highly conjugated anils are to acids. Cyclisation of the anil (VII) to 2′-(p-*nitrophenyl*)-2 : 6′-*diquinolyl* (IX; R = NO_2) was effected by hydrochloric acid at 175° in a sealed tube or, more conveniently, by prolonged boiling with arsenic pentoxide in 60% sulphuric acid.



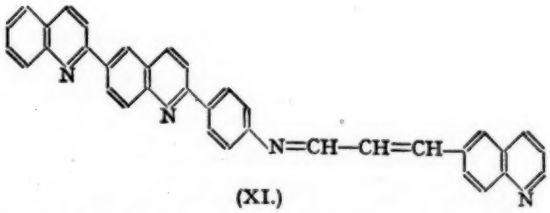
(VIII.)



(IX.)



(X.)



(XI.)

The low solubility and basic properties of the nitro-compound (IX; R = NO_2) rendered its reduction awkward since under ordinary conditions stannous chloride gave a mixture of insoluble stannichlorides whose decomposition yielded a difficultly separable mixture of bases. 2′-(p-*Aminophenyl*)-2 : 6′-*diquinolyl* (IX; R = NH_2) was, however, prepared in good yield by continuous extraction of the nitro-compound (IX; R = NO_2) with a solution of stannous

chloride in 20% hydrochloric acid. Condensation of the amine (IX; R = NH_2) with the quinolylacraldehyde (V) in hydrochloric acid at 150° gave 2 : 6′-*tetraquinolyl* (X), a colourless solid fairly soluble in hot quinoline. When this condensation was effected in dioxan, 2′-[4″-(6‴-*quinolyl*-β-*acrylidene*)*aminophenyl*]-2 : 6′-*diquinolyl* (XI) was isolated.

Experimental.

2-(p-*Acetamidophenyl*)*quinoline*-4-*carboxylic Acid* (I; R = CO_2H, R′ = COMe).—*p*-Acetamidobenzaldehyde (8 g.), freshly-distilled pyruvic acid (3·46 c.c.), and aniline (4·5 c.c.) were refluxed in ethanol (100 c.c.) for 2 hours and kept overnight. The *quinoline* (5·4 g.) separated as a dihydrate which crystallised from ethanol in yellow prisms, m. p. 278—279° (decomp.) (Found : C, 63·2; H, 5·1; N, 8·25. $C_{18}H_{14}O_3N_2,2H_2O$ requires C, 63·1; H, 5·3; N, 8·2%).

The amine (I; R = CO_2H, R′ = H) was prepared in 92% yield by the condensation of *p*-acetamidoacetophenone (14·3 g.) with isatin (11·9 g.) in 50% aqueous potassium hydroxide (36 c.c.); acetylation with acetic anhydride in acetic acid gave the acetamido-compound (I; R = CO_2H, R′ = COMe) identical with that prepared above.

Decarboxylation of the amino-acid (I; R = CO_2H, R′ = H) gave the amine (I; R = R′ = H) (John, *loc. cit.*), from which a *benzylidene* derivative was prepared, crystallising from propanol in colourless leaflets, m. p. 156° (Found : C, 85·3; H, 5·2; N, 9·7. $C_{22}H_{16}N_2$ requires C, 85·7; H, 5·2; N, 9·1%).

Ethyl Quinoline-6-*carboxylate* (II; R = OEt).—*p*-Aminobenzoic acid (55 g.), *p*-nitrobenzoic acid (42·6 g.), ferrous sulphate (14 g.), boric acid (24 g.), glycerol (188 g.), and concentrated sulphuric acid (70 c.c.) were refluxed for 20 hours. The mixture was diluted with water, basified with 5N-sodium hydroxide, filtered, and the filtrate acidified with acetic acid and kept at 0°. The crude, acetone-washed acid (90 g.) was refluxed with ethanol (650 c.c.) and concentrated sulphuric acid (110 c.c.) for 5 hours and the solution concentrated; after dilution with water and basification, the ester was isolated with chloroform and distilled, b. p. 130—150°/2 mm., m. p. 56°, yield 78 g., 60% (Found : N, 7·2. Calc. for $C_{12}H_{11}O_2N$: N, 7·0%).

6-*Acetylquinoline* (II; R = Me).—Ethyl acetate (7·2 c.c.) and ethyl quinoline-6-carboxylate (10 g.) were added to sodium ethoxide (5·07 g.) in benzene (8 c.c.); the mixture was refluxed for 18 hours, and poured on N-sodium hydroxide (10 c.c.), ice (10 g.), and ether (10 c.c.). The yellow solid was collected, and the aqueous layer of the filtrate acidified with carbon dioxide and extracted with ether. The residue after distillation of the ether was added to the yellow solid and heated with 17% hydrochloric acid at 100° for 1½ hours. After basifying with aqueous potassium carbonate, the *ketone* was isolated with ether and distilled, b. p. 145°/2 mm., yield 4·4 g., 52%; it crystallised from light petroleum in colourless rhombs, m. p. 77° (Found : C, 77·2; H, 5·2; N, 8·5. $C_{11}H_9ON$ requires C, 76·9; H, 5·3; N, 8·2%).

2 : 6′-*Diquinolyl*-4-*carboxylic Acid* (III; R = CO_2H).—6-Acetylquinoline (3·4 g.), isatin (2·9 g.), and potassium hydroxide (4·5 g.) in water (12 c.c.) and ethanol (20 c.c.) were boiled under reflux for 6 hours, the ethanol distilled off, and the solution diluted and acidified with acetic acid; the *acid* separated (yield 4·9 g., 82%) and crystallised from quinoline in colourless rhombs, m. p. 334° (decomp.) (Found : C, 76·5; H, 4·3; N, 9·7. $C_{19}H_{12}O_2N_2$ requires C, 76·0; H, 4·0; N, 9·3%).

2 : 6′-*Diquinolyl* (III; R = H).—2 : 6′-Diquinolyl-4-carboxylic acid (4·9 g.) was powdered with copper carbonate (0·5 g.) and the mixture heated till the effervescence ceased. The product was distilled, b. p. 210—250°/3 mm., and the diquinolyl solidified (yield 3·4 g., 81%), m. p. 144° (Weidel, *loc. cit.*, gives m. p. 144°) (Found : C, 84·4; H, 4·7; N, 11·3. Calc. for $C_{18}H_{12}N_2$: C, 84·3; H, 4·7; N, 10·9%).

2-(p-*Oximinoacetamidophenyl*)*quinoline*-4-*carboxylic Acid* (I; R = CO_2H, R′ = CO·CH:NOH).—2-(*p*-Aminophenyl)quinoline-4-carboxylic acid (8·8 g.) in concentrated hydrochloric acid (3·4 c.c.) and water (40 c.c.) was added to chloral hydrate (6 g.) in water (60 c.c.) and ethanol (60 c.c.); hydroxylamine hydrochloride (7·2 g.) was then added and the mixture boiled gently for 35 minutes and vigorously for 5 minutes, cooled, and neutralised with aqueous sodium hydroxide. The *product* separated and crystallised from pyridine–ethanol in yellow needles, m. p. 257—258° (decomp.) (yield 4·6 g., 38%) (Found : C, 64·3; H, 4·0; N, 12·7. $C_{18}H_{13}O_4N_3$ requires C, 64·5; H, 3·9; N, 12·5%).

β-6-*Quinolylacraldehyde* (V).—Acetaldehyde (1·5 c.c.) in water (20 c.c.) was added to quinoline-6-aldehyde (2·6 g.) in benzene (10 c.c.) and aqueous sodium hydroxide (8 c.c.; 5·7%), and the mixture stirred at 3° for 3 hours. The *aldehyde* separated, was triturated under ethanol, and then recrystallised from ethanol, yield 1 g., 33%, m. p. 162—163° (Found : C, 78·8; H, 5·1; N, 7·9. $C_{12}H_9ON$ requires C, 78·7; H, 5·0; N, 7·6%). Other conditions, such as the use of aqueous alcohol as solvent, for this condensation gave no pure product.

2 : 6′-*Triquinolyl* (VI).—β-6-Quinolylacraldehyde (0·37 g.), 2-(*p*-aminophenyl)quinoline (0·48 g.), and concentrated hydrochloric acid (5 c.c.) were heated together in a sealed tube at 150° for 5 hours. Dilute hydrochloric acid was added, the solution filtered, the filtrate basified, and the brown powder collected. After trituration with ethanol, the residual *triquinolyl* crystallised from quinoline in colourless plates (0·027 g.), m. p. 267—269°; high-vacuum sublimation did not raise the m. p. (Found : C, 84·45; H, 4·6; N, 11·1. $C_{27}H_{17}N_3$ requires C, 84·6; H, 4·5; N, 11·0%).

p-*Nitrocinnamaldehyde*.—Methanolic potassium hydroxide (3·5 c.c.; 25%) was added dropwise to a vigorously-stirred suspension of finely-powdered *p*-nitrobenzaldehyde (75 g.) in freshly-distilled acetaldehyde (185 c.c.); the mixture was kept at 5—7° during the addition. Acetic anhydride (120 c.c.) was added, the solution heated to 120° for 1 hour, poured into water (450 c.c.), and, after the addition of 4·35N-hydrochloric acid (180 c.c.), refluxed for 30 minutes. The next day, the nitrocinnamaldehyde was collected, washed with water, and recrystallised from ethanol (64·7 g., 72%), m. p. 140—141°.

2-[4′-(p-*Nitrocinnamylidene*)*aminophenyl*]*quinoline* (VII).—(*a*) *p*-Nitrocinnamaldehyde (4·2 g.) was added to 2-(*p*-aminophenyl)quinoline (6·3 g.) in concentrated hydrochloric acid (12 c.c.); after the addition of further concentrated hydrochloric acid (5 c.c.) the mixture was refluxed for 5 hours. Extrac-

tion with hot concentrated hydrochloric acid (40 c.c.) left a yellow solid which was added to aqueous sodium hydrogen carbonate, the mixture heated, and the solid collected and washed with hot ethanol (200 c.c.). Recrystallisation from 90% dioxan–water, then twice from amyl acetate gave the *anil* (2·6 g., 29%) as orange plates, m. p. 211—214° (decomp.) (Found: C, 76·1; H, 4·3; N, 11·2. $C_{24}H_{17}O_2N_3$ requires C, 76·0; H, 4·5; N, 11·1%). Heating with 2 : 4-dinitrophenylhydrazine in dilute sulphuric acid gave p-*nitrocinnamaldehyde dinitrophenylhydrazone* (VIII), m. p. 267—268° (decomp.), mixed m. p. with a sample prepared directly from the aldehyde, 271° (decomp.). This sample crystallised from nitrobenzene–amyl alcohol in scarlet needles, m. p. 273° (decomp.) (Found: C, 50·6; H, 3·2; N, 19·7. $C_{15}H_{11}O_6N_5$ requires C, 50·4; H, 3·1; N, 19·6%).

(*b*) *p*-Nitrocinnamaldehyde (40·2 g.) in hot ethanol (525 c.c.) was added to 2-(*p*-aminophenyl)-quinoline (50 g.) in hot ethanol (525 c.c.), the solution refluxed for 3½ hours, kept overnight, and the solid collected (78 g.). It had m. p. and mixed m. p. with the product of method (*a*) of 210—212° (decomp.).

2′-(p-*Nitrophenyl*)-2 : 6′-*diquinolyl* (IX; R = NO_2).—2-[4′-(*p*-Nitrocinnamylidene)aminophenyl]-quinoline (72 g.), arsenic pentoxide (21·6 g.), and 60% sulphuric acid (240 c.c.) were refluxed together for 12 hours, the mixture diluted with an equal volume of water, decanted from tar, cooled, and basified with 5N-sodium hydroxide. The brown solid was collected and extracted with hot amyl acetate (2000 c.c.); the *diquinolyl* which separated crystallised from *cyclo*hexanone in buff needles, m. p. 266—268° (decomp.) (yield 4·5 g., 6%) (Found: C, 76·6; H, 4·2; N, 11·0. $C_{24}H_{15}O_2N_3$ requires C, 76·4; H, 4·0; N, 11·1%). The yield was lower when more concentrated sulphuric acid was used, and no product could be isolated when the arsenic pentoxide was omitted.

The reaction could also be carried out by heating the anil (6 g.) in concentrated hydrochloric acid (15 c.c.) for 5 hours at 175° in a sealed tube; the yield was 4% and was not improved by the addition of arsenic pentoxide.

2′-(p-*Aminophenyl*)-2 : 6′-*diquinolyl* (IX; R = NH_2).—2′-(*p*-Nitrophenyl)-2 : 6′-diquinolyl (2 g.) was extracted in an all-glass Soxhlet apparatus with 20% hydrochloric acid (50 c.c.) containing stannous chloride (4 g.). The red solid was collected and decomposed with hot 5N-sodium hydroxide; the *amine* crystallised from much 70% dioxan–water in yellow acicular plates, m. p. 234° (yield 1·16 g., 63%) (Found: C, 82·8; H, 5·15; N, 12·25. $C_{24}H_{17}N_3$ requires C, 83·0; H, 4·9; N, 12·1%). The solution of the amine in acetic acid was deep red, and dilute solutions in organic solvents showed a blue fluorescence.

2 : 6′-*Tetraquinolyl* (X).—β-6-Quinolylacraldehyde (0·28 g.) was added to 2′-(*p*-aminophenyl)-2 : 6′-diquinolyl (0·54 g.) in concentrated hydrochloric acid (4·3 c.c.) and, after the addition of further concentrated hydrochloric acid (4·3 c.c.), the mixture was heated in a sealed tube at 150° for 5 hours. Dilute hydrochloric acid (4 c.c.) was added, and the red solid collected, washed with 8N-hydrochloric acid, and treated with aqueous ammonia. The yellow material was digested with hot dioxan; the residual *tetraquinolyl* crystallised from quinoline in colourless leaflets (0·035 g.), m. p. 348—350° (evacuated capillary) (Found: C, 84·5; H, 4·3; N, 11·1. $C_{36}H_{22}N_4$ requires C, 84·7; H, 4·3; N, 11·0%).

2′-[4″-(6‴-*Quinolyl*-β-*acrylidene*)*aminophenyl*]-2 : 6′-*diquinolyl* (XI).—β-6-Quinolylacraldehyde (0·13 g.) was added to 2′-(*p*-aminophenyl)-2 : 6′-diquinolyl (0·25 g.) in dioxan (12 c.c.) and acetic acid (1·5 c.c.). After 2 hours' heating, the *anil* separated (0·27 g.), and crystallised from pyridine in yellow prisms, m. p. 248—249° (decomp.) (Found: C, 84·0; H, 4·9; N, 11·1. $C_{36}H_{24}N_4$ requires C, 84·3; H, 4·7; N, 10·9%).

The author thanks Mr. G. Ingram for micro-analyses and Mr. K. Blau for technical assistance.

COURTAULDS, LIMITED, MAIDENHEAD. [*Received, January 17th*, 1948.]

---

407. *Synthesis of Piperidine Derivatives. Part II. Aryldecahydroquinolines.*

By G. M. BADGER, J. W. COOK, and THOMAS WALKER.

As part of a scheme to prepare new pharmacologically active bases, 4-*phenyl*- and 4-p-*methoxyphenyl*-1-*ethyldecahydroquinolines* have been synthesised by hydrogenation in ethanolic solution over copper chromite of the *oximes* of ethyl β-2-keto*cyclo*hexyl-β-phenyl- and -β-*p*-methoxyphenyl-propionate. Condensation of 2-benzylidene*cyclo*hexanone with ethyl sodiomalonate gave, not the expected malonic ester (III; Ar = Ph, R = Et) but a *lactone* (V; Ar = Ph) derived from it by loss of ethanol. Some transformations of this lactone are described. 2-*p*-Methoxybenzylidene*cyclo*hexanone reacted similarly with ethyl sodiomalonate.

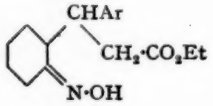
IN recent years a number of new synthetic analgesics have been described. Two outstanding examples are pethidine (a piperidine derivative) and amidone (a basic derivative of diphenylmethane). Thorp, Walton, and Ofner (*Nature*, 1947, **160**, 605) have reported that (−)-amidone has about twice the analgesic activity of morphine (compare Scott and Chen, *J. Pharm. Exp. Ther.*, 1946, **87**, 63). Like morphine, both pethidine and amidone appear to produce drug-addiction, and a satisfactory analgesic free from this undesirable side-effect has not yet been found. Possibly the two effects are inseparable, but this can only be determined by

examining a sufficient number of new products. Other analgesics structurally related to pethidine have been examined pharmacologically by, for example, Jensen and Lundquist (*Dansk Tidsskr. Farm.*, 1943, **17**, 173) and MacDonald *et al.* (*Brit. J. Pharmacol.*, 1946, **1**, 4).

Among the more efficient of the newer antispasmodics are the diethylaminoethyl esters of diphenylacetic acid (trasentin), *cyclo*hexylphenylacetic acid (trasentin 6H), fluorene-9-carboxylic acid (pavatrine), and 9 : 10-dihydroanthracene-9-carboxylic acid (see Blicke, *Ann. Rev. Biochem.*, 1944, **13**, 549). Relatively simple piperidine derivatives are also known to have antispasmodic activity (Cerkovnikov and Prelog, *Ber.*, 1941, **74**, 1648; Fellows and Cunningham, *Federation Proc.*, 1942, **1**, 151; Lee and Freudenberg, *J. Org. Chem.*, 1944, **9**, 537; Foster, Moench, and Clark, *J. Pharm. Exp. Ther.*, 1946, **87**, 73; Kwartler and Lucas, *J. Amer. Chem. Soc.*, 1947, 69, 2582), and Dr. J. D. P. Graham has found (unpublished experiments) that some of the piperidine bases synthesised by Barr and Cook (*J.*, 1945, 438) have marked antispasmodic properties: the hydrochloride of 3 : 4-diphenyl-1-methylpiperidine, for example, has high musculotropic activity. It seems that all the efficient antispasmodics, although varying widely in molecular structure, are salts of strong tertiary bases, and this may be an important requirement for this type of pharmacological action.

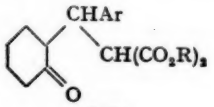
In Part I of this series, Barr and Cook (*loc. cit.*) described the synthesis of 3 : 4-diaryl-1-alkylpiperidines by copper chromite hydrogenation of appropriate γ-cyano-esters in alcoholic solvents, which supplied the *N*-alkyl substituents. The present communication describes the synthesis, by a somewhat analogous method, of decahydroquinoline derivatives which are being examined for analgesic and antispasmodic action by Dr. J. D. P. Graham, who will publish his results elsewhere.

The *oxime* (I; Ar = Ph) of ethyl β-2-keto*cyclo*hexyl-β-phenylpropionate (Vorländer and Kunze, *Ber.*, 1926, **59**, 2078) was hydrogenated in ethanolic solution over copper chromite to give *4-phenyl-1-ethyldecahydroquinoline* (II; Ar = Ph). For this structure four optically inactive stereoisomeric forms are possible, but the liquid base, obtained in satisfactory yield, gave a well-crystallised *picrate* and appeared to be stereochemically homogeneous. In view of the high temperature used for hydrogenation it probably belongs to the *trans*-decahydroquinoline series. 4-p-*Methoxyphenyl*-1-*ethyldecahydroquinoline* (II; Ar = *p*-C_6H_4·OMe), similarly prepared from the *oxime* (I; Ar = *p*-C_6H_4·OMe), was a crystalline solid, and it also was formed free, or almost free, from stereoisomerides. By being heated with hydrobromic acid in acetic acid the latter base was demethylated to the *hydrobromide* of 4-*p*-hydroxyphenyl-1-ethyldecahydroquinoline. 4-Phenyl-1-ethyldecahydroquinoline was completely dehydrogenated by being heated with palladium black, the *N*-ethyl group being eliminated, with formation of the known 4-phenylquinoline (Königs and Nef, *Ber.*, 1886, **19**, 2430; Koenigs and Meimberg, *Ber.*, 1895, **28**, 1039).



(I.)

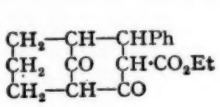
(II.)



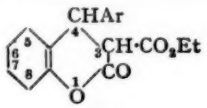
(III.)

An obvious route to the keto-acid required for the preparation of the oxime (I; Ar = Ph) was the condensation of 2-benzylidene*cyclo*hexanone with ethyl sodiomalonate followed by hydrolysis of the product and then thermal decarboxylation. This Michael reaction was described by Vorländer and Kunze (*loc. cit.*) who allowed a suspension of ethyl sodiomalonate in benzene or ether to react with the unsaturated ketone at room temperature during two days. They obtained a liquid product which was assumed to be ethyl β-2-keto*cyclo*hexylbenzylmalonate (III; Ar = Ph, R = Et), as it was hydrolysed to the malonic acid and converted by concentrated ammonia into the corresponding diamide. By carrying out the Michael reaction in boiling benzene (2 hours) we obtained, not the liquid ester of Vorländer and Kunze, but a crystalline compound which was shown by elementary analysis and ethoxyl determination to have been formed from the diester (III) by loss of a molecule of ethanol. Our product was insoluble in cold aqueous sodium hydroxide, but was readily hydrolysed by boiling alkali to the malonic acid (III; Ar = Ph, R = H). Elimination of ethanol from the diester (III; Ar = Ph, R = Et) by means of sodium ethoxide could give the strainless *bicyclo*nonane derivative (IV) (cf. Rabe, *Ber.*, 1903, **36**, 225, 227; 1904, **37**, 1671), but the product gave no colour with ferric chloride, rapidly decolourised bromine water, and reduced ammoniacal silver solution. These and other reactions indicate that it is an unsaturated lactone, namely, *ethyl* 4-*phenyl*-3 : 4 : 5 : 6 : 7 : 8-

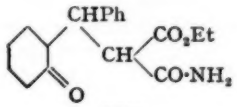
hexahydrocoumarin*-3-*carboxylate (V; Ar = Ph). The position of the ethylenic bond has not been established, but on general grounds the position shown is probable.



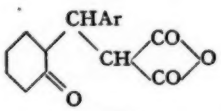
(IV.)



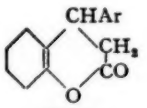
(V.)



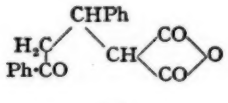
(VI.)



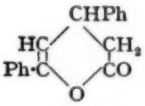
(VII.)



(VIII.)



(IX.)



(X.)

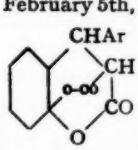
When an ethanolic solution of the carbethoxy-lactone (V; Ar = Ph) was treated with concentrated aqueous ammonia the lactone ring was opened with formation of ***α-carbethoxy*-β-2-*keto*cyclo*hexyl*-β-*phenylpropionamide*** (VI). Similar production of an amide of a keto-acid by the action of ammonia on an unsaturated δ-lactone (X) was recorded by Mannich and Butz (*Ber.*, 1929, **62**, 456). We also obtained the monoamide (VI) by treatment of the diester (III; Ar = Ph, R = Et) with ethanolic ammonia. This result is at variance with the work of Vorländer and Kunze (*loc. cit.*) who obtained the diamide from their crude diester (III; Ar = Ph, R = Et). Possibly the explanation of the discrepancy is that in the concentration which we used the monoamide crystallised as soon as it was formed.

By the action of concentrated sulphuric acid the carbethoxy-lactone (V; Ar = Ph) was converted into **β-2-*keto*cyclo*hexylbenzylmalonic anhydride*** (VII; Ar = Ph). This well-crystallised anhydride was remarkably stable and could be distilled under reduced pressure without decomposition. It was hydrolysed by hot dilute alkali to the malonic acid (III; Ar = Ph, R = H), which was reconverted into the anhydride by treatment with thionyl chloride in benzene. Concentrated sulphuric acid did not dehydrate either the malonic acid or its diethyl ester. Possibly the action of sulphuric acid on the carbethoxy-lactone involves addition of sulphuric acid followed by elimination of ethyl hydrogen sulphate.*

Anhydrides of simple dialkylmalonic acids were prepared by Einhorn (*Annalen*, 1908, **359**, 145) who found them to be polymeric and amorphous; Staudinger and Ott (*Ber.*, 1908, **41**, 2208) showed that they lost carbon dioxide when heated and gave ketens. The malonic anhydride (VII; Ar = Ph) contrasted strikingly with the anhydrides of Einhorn and Staudinger, not only in being crystalline and monomeric and capable of crystallisation from ethanol, but also in its behaviour on thermal treatment. This led to loss of carbon dioxide and formation of ***4-phenyl*-3 : 4 : 5 : 6 : 7 : 8-*hexahydrocoumarin*** (VIII; Ar = Ph). Some analogous examples have been described by Mannich and Butz (*loc. cit.*) who found, for example, that the anhydride (IX) lost carbon dioxide when heated and was converted into the unsaturated lactone (X). Probably a determining factor in these transformations is the presence of a carbonyl group so situated as to permit lactone formation.

The literature contains little reference to the action of ketonic reagents on unsaturated

* *Added, June* 29th, 1948.—When this paper was read at a meeting of the Chemical Society on February 5th, 1948, it was suggested by Dr. A. J. Birch (see *Chem. and Ind.*, 1948, 156; similar suggestions were subsequently sent to us by Dr. S. H. Harper and Dr. C. W. Shoppee) that the compounds described as malonic anhydrides are in reality dilactones, and that structure (VII) should be replaced by the formula inset.

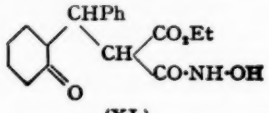


We accept this suggestion, for the properties of the compounds in question are in better accord with a dilactone structure than a malonic anhydride structure, although it is by no means easy to distinguish between them experimentally. We have attempted this in a number of ways. The only experiment which has given decisive results was the hydrogenation of the phenyl dilactone (m. p. 169°) over Adams's platinum catalyst in acetic acid solution. This led to the uptake of 2·8 mols. of hydrogen and the formation of the corresponding *cyclo*hexyl dilactone (in which Ar in the inset formula becomes C_6H_{11}). This ***hexahydride*** formed colourless needles (from ethanol), m. p. 137° (Found: C, 68·9; H, 7·75. $C_{16}H_{22}O_4$ requires C, 69·1; H, 7·9%). Hydrolysis with sodium hydroxide solution gave a sparingly soluble sodium salt; the acid regenerated from this could not be obtained pure, as on repeated recrystallisation it reverted to the dilactone, m. p. 137°.

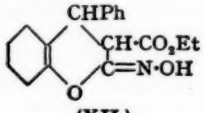
We regard this as evidence in favour of the dilactone structure given above in preference to (VII), for the reason that it is inconceivable that a carbonyl group (as in VII) could have resisted hydrogenation under conditions which led to reduction of phenyl to *cyclo*hexyl. A corollary of this conclusion is that the malonic anhydrides of Mannich and Butz (*loc. cit.*) (*e.g.*, IX) have similar dilactone structures. Analogous dilactones have been described by Qudrat-i-Khuda (*J.*, 1929, 201, 713).

lactones, although it is well known that saturated lactones react with phenylhydrazine to give phenylhydrazides of the corresponding hydroxy-acids. However, Minunni, Ottaviano, and Spina (*Gazzetta*, **1929**, **59**, 116), in attempting to remove the arylidene group from α-arylidene-aminocinnamo-β-lactones with phenylhydrazine, found that the lactone ring was opened with formation of the phenylhydrazide of α-amino-β-hydroxycinnamic acid. The lactone ring was not affected by hydroxylamine. When the hexahydrocoumarin (V; Ar = Ph) was treated with 2 : 4-dinitrophenylhydrazine in ethanol there was obtained a heavy red oil, from which was isolated a small amount of the crystalline 2 : 4-*dinitrophenylhydrazone* of ethyl β-2-keto*cyclo*hexylbenzylmalonate (III; Ar = Ph, R = Et). The same dinitrophenylhydrazone was obtained directly from this ester. Its formation from the lactonic-ester was evidently due to opening of the lactone ring by addition of ethanol. A similar reaction was observed by Mannich and Butz (*loc. cit.*), who found that boiling methanol converted the unsaturated lactone (X) into the methyl ester of the corresponding keto-acid.

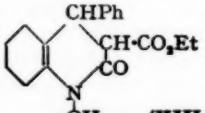
The lactonic ester (V; Ar = Ph) reacted with hydroxylamine as it did with ammonia, for the product was a *hydroxamic acid* (XI). It was insoluble in sodium carbonate solution but soluble in aqueous sodium hydroxide and it gave a deep red colouration with ferric chloride. Unlike many hydroxamic acids, our compound (XI) did not reduce Fehling's solution (compare Yale, *Chem. Reviews*, **1943**, **33**, 209), but it reduced hot ammoniacal silver nitrate solution. The hydroxamic acid (XI) lost the elements of water above its m. p. to form a compound for which we suggest the structure (XII) or, more probably, (XIII). Hydroxamic acids usually undergo the Lossen rearrangement when heated, but it was clear that our product of thermal dehydration was neither a primary nor a secondary product of such a rearrangement. It still contained the carbon skeleton of the hydroxamic acid, for treatment with 2 : 4-dinitrophenylhydrazine gave a small amount of the 2 : 4-dinitrophenylhydrazone of (III; Ar = Ph, R = Et). The dehydration product (XII or XIII) was insoluble in sodium carbonate solution but soluble in sodium hydroxide solution, and gave a purple colour with ferric chloride. Treatment with hot aqueous alkali hydrolysed the carbethoxy-group and gave an *acid* which likewise gave a colour with ferric chloride. This acid was decarboxylated at its m. p. to an oil which did not crystallise.



(XI.)



(XII.)



(XIII.)

A parallel series of experiments to that described above was carried out using as the starting point 2-*p*-methoxybenzylidene*cyclo*hexanone. This reacted with ethyl sodiomalonate in boiling benzene to give a product which was not obtained crystalline, but it evidently consisted essentially of the anticipated hexahydrocoumarin (V; Ar = *p*-C_6H_4·OMe). This reacted with concentrated sulphuric acid to give, in excellent yield, β-2-*keto*cyclo*hexyl*-p-*methoxybenzylmalonic anhydride* (VII; Ar = *p*-C_6H_4·OMe). The latter, on heating, lost carbon dioxide and gave 4-p-*methoxyphenyl*-3 : 4 : 5 : 6 : 7 : 8-*hexahydrocoumarin* (VIII; Ar = *p*-C_6H_4·OMe). The same compound was obtained from the crude carbethoxy-lactone (V; Ar = *p*-C_6H_4·OMe) when purification was attempted by vacuum distillation. Hydrolysis of the anhydride (VII; Ar = *p*-C_6H_4·OMe) gave β-2-*keto*cyclo*hexyl*-p-*methoxybenzylmalonic acid* (III; Ar = *p*-C_6H_4·OMe, R = H), which was also formed by hydrolysis of the crude carbethoxy-lactone (V; Ar = *p*-C_6H_4·OMe). Decarboxylation of the malonic acid gave β-2-*keto*cyclo*hexyl*-β-p-*methoxyphenylpropionic acid* which was esterified and the crude ester oximated to give (I; Ar = *p*-C_6H_4·OMe). The crude ester could not be purified by distillation as it decomposed to the lactone (VIII; Ar = *p*-C_6H_4·OMe).

Experimental.

Ethyl 4-*Phenyl*-3 : 4 : 5 : 6 : 7 : 8-*hexahydrocoumarin*-3-*carboxylate* (V; Ar = Ph).—2-Benzylidene-*cyclo*hexanone (Poggi and Guastalla, *Gazzetta*, 1931, **61**, 405; cf. Vorländer and Kunze, *loc. cit.*) (35·7 g. in benzene (100 c.c.) was added all at once to a suspension of ethyl sodiomalonate [from sodium (4·33 g.) and ethyl malonate (30·1 g.)] in benzene (150 c.c.), and the mixture was refluxed for 2 hours. The cooled solution was shaken with ice-cold dilute sulphuric acid, washed with water, sodium carbonate solution, and then water, and dried. After removal of the benzene and a little unchanged ethyl malonate, the resulting oil was dissolved in warm ethanol. On cooling, *ethyl* 4-*phenyl*-3 : 4 : 5 : 6 : 7 : 8-*hexahydrocoumarin*-3-*carboxylate* (42 g.) separated. It formed colourless needles (from *cyclo*hexane), m. p. 69° (Found : C, 72·1; H, 6·6; OEt, 15·4. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7; OEt, 15·0%). A further quantity (8 g.) was obtained by distilling (b. p. 185°/1 mm.) the residue from the alcoholic mother liquor.

β-2-*Keto*cyclo*hexylbenzylmalonic Acid* (III; Ar = Ph, R = H).—The above hexahydrocoumarin

(22 g.) was hydrolysed by 1½ hours' refluxing with excess of 40% aqueous alcoholic potassium hydroxide. The crude oily malonic acid solidified on standing in the refrigerator, and, after recrystallisation from 50% aqueous ethanol, formed colourless needles, m. p. 135° (Vorländer and Kunze, *loc. cit.*, give m. p. 135—136°).

Ethyl β-2-Ketocyclohexylbenzylmalonate (III; Ar = Ph, R = Et).—The above ketocyclohexylbenzylmalonic acid (3 g.) was esterified by passing dry hydrogen chloride into its solution in absolute ethanol. *Ethyl β-2-ketocyclohexylbenzylmalonate* (3 g.) was obtained as a colourless viscous oil, b. p. 172° (air-bath)/1 mm. (Found: C, 70·1; H, 7·4. $C_{20}H_{26}O_5$ requires C, 69·4; H, 7·5%).

The 2 : 4-*dinitrophenylhydrazone*, prepared in ethanol, gave orange needles (from ethanol), m. p. 135—136° (Found: C, 59·2; H, 5·7; N, 10·7. $C_{26}H_{30}O_8N_4$ requires C, 59·3; H, 5·7; N, 10·6%).

α-Carbethoxy-β-2-ketocyclohexyl-β-phenylpropionamide (VI).—(*a*) Concentrated ammonia was added to a hot solution of ethyl 4-phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate in ethanol until a faint turbidity appeared. Sufficient hot ethanol was then added to give a clear solution, and the mixture placed in the refrigerator. After 2 days, crystalline *α-carbethoxy-β-2-ketocyclohexyl-β-phenylpropionamide* was obtained. It formed colourless needles (from ethanol), m. p. 183° (decomp.) (Found: C, 68·1; H, 7·2; N, 4·4. $C_{18}H_{23}O_4N$ requires C, 68·1; H, 7·25; N, 4·4%).

(*b*) A solution of ethyl β-2-ketocyclohexylbenzylmalonate in ethanol, treated with concentrated ammonia as above, gave the same monoamide, m. p. and mixed m. p. 183° (decomp.).

β-2-Ketocyclohexylbenzylmalonic Anhydride (VII; Ar = Ph).—Concentrated sulphuric acid (3 c.c.) was added to ethyl 4-phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate (2 g.) in a test tube. A deep red solution resulted with the evolution of considerable heat. The mixture was stirred with a glass rod, heated on the steam-bath for 1 minute, and then immediately cooled in ice. After being poured into ice-cold water, the product separated as an oil which was washed with water and treated with a little ethanol. The resulting crystalline *β-2-ketocyclohexylbenzylmalonic anhydride* (1·6 g.) formed colourless needles (from ethanol), m. p. 169° (decomp.) (Found: C, 70·6; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). The best yields in this preparation were obtained only when small quantities, as above, were used, the reaction then being more easily controllable.

This anhydride was also formed when the malonic acid (III; Ar = Ph, R = H) was heated with thionyl chloride in benzene, a procedure used by Mannich and Butz (*loc. cit.*) for the preparation of malonic anhydrides of analogous structure. It boiled without decomposition at 160°/0·4 mm., the distillate being a colourless liquid which rapidly solidified. After recrystallisation from ethanol this had m. p. 169°, alone or mixed with an undistilled specimen.

By refluxing with excess of 10% aqueous sodium hydroxide until all went into solution, the anhydride (0·2 g.) was hydrolysed to β-2-ketocyclohexylbenzylmalonic acid (0·2 g.), m. p. and mixed m. p. 135°.

4-Phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin (VIII; Ar = Ph).—This was obtained by heating the pure anhydride (VII; Ar = Ph) over a free flame until gas evolution ceased. The residual liquid was distilled at 160°/1 mm., a sample being redistilled for analysis. *4-Phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin* formed a colourless viscous liquid, b. p. 154°/0·3 mm. (Found: C, 78·6; H, 7·1. $C_{15}H_{16}O_2$ requires C, 78·8; H, 7·0%).

This hexahydrocoumarin (0·1 g.) was hydrolysed to β-2-ketocyclohexyl-β-phenylpropionic acid (0·1 g.) by refluxing with 10% aqueous sodium hydroxide until all went into solution. The product had m. p. 125°, not depressed by an authentic specimen obtained by decarboxylation of β-2-ketocyclohexylbenzylmalonic acid by the method of Vorländer and Kunze (*loc. cit.*).

Action of Dinitrophenylhydrazine on Ethyl 4-Phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate.—A solution of the carbethoxy-lactone in ethanol was treated with excess of 2 : 4-dinitrophenylhydrazine solution. After several hours, the supernatant liquid was decanted and the heavy red oil which had separated was dissolved in ethanol. On cooling in ice a few orange-yellow crystals of the dinitrophenylhydrazone of ethyl β-2-ketocyclohexylbenzylmalonate separated. After recrystallisation, the product had m. p. 135°, not depressed by an authentic specimen (above).

Action of Hydroxylamine on Ethyl 4-Phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate.—A solution of the hexahydrocoumarin (3·3 g.) in ethanol (15 c.c.) was treated with a solution of hydroxylamine hydrochloride (1 g.) and anhydrous sodium acetate (2 g.) in a little water, and left overnight. Water (15 c.c.) was added, and the mixture cooled in the refrigerator. The solid (3 g.) was collected, dried on a porous plate and in a vacuum desiccator, and then recrystallised from benzene–light petroleum (b. p. 60—80°). The *hydroxamic acid* (XI) formed small colourless needles, m. p. 138° (decomp.) (Found: C, 65·1; H, 6·7; N, 4·4. $C_{15}H_{23}O_3N$ requires C, 64·9; H, 6·9; N, 4·2%).

This hydroxamic acid (1 g.) was heated at 145° (bath temp.) for 5 minutes. A solution of the residual oil, in a little ethanol, deposited colourless crystals of a *substance* (probably XIII) (0·75 g.) which after recrystallisation from ethanol formed colourless needles, m. p. 154° (Found: C, 68·7; H, 6·3; N, 4·4. $C_{15}H_{21}O_4N$ requires C, 68·6; H, 6·65; N, 4·4%). A solution of this product in ethanol was treated with excess of 2 : 4-dinitrophenylhydrazine solution. After a week, a few orange-yellow crystals were collected; these, after several recrystallisations from ethanol, were identified as the 2 : 4-dinitrophenylhydrazone of ethyl β-2-ketocyclohexylbenzylmalonate, m. p. and mixed m. p. 135°.

The substance (m. p. 154°, 1·5 g.) was warmed with excess of 40% aqueous potassium hydroxide at 80° for ½ hour. The cooled solution, diluted with a little water, was acidified with dilute hydrochloric acid and extracted with ether. The oil obtained on distillation of the ether was dissolved in dry benzene, from which a crystalline *acid* (0·9 g.) separated; it formed very small needles, m. p. 146—147° (from benzene) (Found: C, 66·8; H, 5·8; N, 4·8. $C_{14}H_{17}O_4N$ requires C, 66·9; H, 5·9; N, 4·9%). This acid lost carbon dioxide at the m. p. to give a viscous oil which did not crystallise.

Oxime of Ethyl β-2-Ketocyclohexyl-β-phenylpropionate (I; Ar = Ph).—A solution of hydroxylamine hydrochloride (3·4 g.) and anhydrous sodium acetate (7 g.) in a little water was added to a solution of ethyl β-2-ketocyclohexyl-β-phenylpropionate (Vorländer and Kunze, *loc. cit.*, 7 g.) in ethanol, and the mixture refluxed for 5 minutes. After several hours at room temperature the solution deposited crystals (7 g.) of the *oxime*, which formed colourless needles (from ethanol), m. p. 126° (Found: C, 70·7; H, 7·9; N, 4·9. $C_{17}H_{23}O_3N$ requires C, 70·6; H, 7·95; N, 4·8%).

4-Phenyl-1-ethyldecahydroquinoline (II; Ar = Ph).—A solution of the above oxime (13 g.) in ethanol (300 c.c.) was reduced with hydrogen and copper chromite (6 g.) (*Org. Synth.*, Coll. Vol. II, p. 142) at 200° and 165 atmospheres for 3 hours. The catalyst was filtered off, the alcohol removed on the steam-bath, and the residual oil dissolved in ether. The ether solution was extracted three times with dilute hydrochloric acid, and washed with water. The hydrochloric acid extracts and washings were neutralised with sodium hydroxide, and the resulting oil was extracted with ether. Distillation gave *4-phenyl-1-ethyldecahydroquinoline* (8 g.) as a colourless liquid, b. p. 134°/1 mm. (Found: C, 84·0; H, 10·45; N, 5·8. $C_{17}H_{25}N$ requires C, 84·0; H, 10·3; N, 5·75%).

The *picrate*, prepared in ethanol, formed yellow needles (from glacial acetic acid), m. p. 204—207° (Found: C, 58·6; H, 6·0. $C_{23}H_{28}O_7N_4$ requires C, 58·4; H, 5·9%). The redistilled base regenerated from the pure picrate did not crystallise. The hydrochloride was very hygroscopic.

Dehydrogenation of 4-Phenyl-1-ethyldecahydroquinoline.—A mixture of the base (0·55 g.) and palladium black (0·07 g.) was heated at 300° for 6 hours in a slow stream of dry carbon dioxide. The resulting oil gave a picrate (0·65 g.) which m. p. and analysis showed to be the picrate of 4-phenylquinoline. It formed small yellow needles (from ethanol), m. p. 226° (Found: C, 58·3; H, 2·9; N, 12·6. Calc. for $C_{15}H_{11}N,C_6H_3O_7N_3$: C, 58·1; H, 3·2; N, 12·9%). For this picrate Koenigs and Meimberg (*loc. cit.*) give m. p. 224°, and Kenner and Statham (*J.*, 1935, 301) give m. p. 225°.

The base regenerated from the pure picrate was distilled at 135°/2 mm.; the distillate did not crystallise,* although Kŏnigs and Nef (*loc. cit.*) give m. p. 61—62° for 4-phenylquinoline. In order to complete the identification, therefore, the following salts were prepared. (*a*) The sulphate had m. p. 193—195° (lit., 195—196°); its aqueous solution fluoresced in ultra-violet light. (*b*) The methiodide formed long yellow needles (from ethanol), m. p. 222° (lit., 222°). (*c*) The chloroplatinate had m. p. 244° (Koenigs and Jaeglé, *Ber.*, 1895, **28**, 1050, give 244°).

Ethyl 4-p-*Methoxyphenyl*-3 : 4 : 5 : 6 : 7 : 8-*hexahydrocoumarin*-3-*carboxylate* (V; Ar = *p*-C_6H_4·OMe).—2-*p*-Methoxybenzylidene*cyclo*hexanone (21·6 g.) (Poggi and Guastalla, *loc. cit.*) in benzene (100 c.c.) was added all at once to a suspension of ethyl sodiomalonate [from sodium (2·3 g.) and ethyl malonate (16 g.)] in benzene (100 c.c.), and the mixture refluxed for 2 hours. After working up as for the benzylidene*cyclo*hexanone condensation, the product (34 g.) was obtained as a heavy viscous oil, which was sufficiently pure for the next stage of the synthesis. In an attempt to prepare a specimen for analysis, the oil (2 g.) was distilled in a vacuum. There was considerable decomposition, and the viscous brown distillate (b. p. 235°/7 mm.) was redistilled, giving a colourless oil (b. p. 190°/1 mm.). A solution of this oil in ethanol deposited crystals of 4-p-*methoxyphenyl*-3 : 4 : 5 : 6 : 7 : 8-*hexahydrocoumarin* (0·4 g.), which after recrystallisation from ethanol formed long colourless needles, m. p. 113° (Found: C, 74·1; H, 6·9. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%).

*β-2-Keto*cyclo*hexyl*-p-*methoxybenzylmalonic Anhydride* (VII; Ar = *p*-C_6H_4·OMe).—Concentrated sulphuric acid (3 c.c.) was added to the crude ethyl 4-*p*-methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate (2 g.). After being heated on the steam-bath for 1 minute, and then cooled in ice, the solution was poured into ice–water. The product, after being washed with water, was dissolved in ethanol (charcoal) from which colourless crystals of *β-2-keto*cyclo*hexyl*-p-*methoxybenzylmalonic anhydride* (1·3 g.) separated. After recrystallisation from ethanol this formed colourless needles, m. p. 154—155° (Found: C, 67·8; H, 6·0. $C_{17}H_{18}O_5$ requires C, 67·55; H, 5·95%). This anhydride (0·5 g.) was converted into 4-*p*-methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin (0·3 g.) by being heated at 160° until evolution of gas had ceased. After recrystallisation this had m. p. and mixed m. p. 113°.

*β-2-Keto*cyclo*hexyl*-p-*methoxybenzylmalonic Acid* (III; Ar = *p*-C_6H_4·OMe; R = H).—(*a*) Ethyl 4-*p*-methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate (24 g.) was hydrolysed by 1½ hours' boiling with 40% aqueous-alcoholic potassium hydroxide. *β-2-Keto*cyclo*hexyl*-p-*methoxybenzylmalonic acid* (15 g.) formed fine colourless needles (from acetic acid), m. p. 130°. Analysis of the specimen dried in a vacuum desiccator showed the presence of one molecule of acetic acid of crystallisation (Found: C, 60·0; H, 6·7. $C_{17}H_{20}O_6,C_2H_4O_2$ requires C, 60·0; H, 6·3%).

(*b*) Keto*cyclo*hexylmethoxybenzylmalonic anhydride (0·2 g.) was hydrolysed to the same keto*cyclo*hexylmethoxybenzylmalonic acid (m. p. and mixed m. p. 130°) by refluxing with excess of 10% aqueous sodium hydroxide.

*β-2-Keto*cyclohexyl-β-p-*methoxyphenylpropionic Acid.*—(*a*) β-2-Keto*cyclo*hexyl-*p*-methoxybenzylmalonic acid (35 g.) was heated at 150° (bath temp.) until evolution of carbon dioxide ceased. The oil obtained was dissolved in ethyl acetate, from which crystalline *β-2-keto*cyclo*hexyl-β-p-methoxyphenylpropionic acid* (25 g.) was obtained. It formed small colourless needles (from ethyl acetate), m. p. 125—126° (Found: C, 69·7; H, 7·2. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·2%).

(*b*) The same acid was obtained by refluxing 4-*p*-methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin with excess of 10% aqueous sodium hydroxide.

*Ethyl β-2-Keto*cyclo*hexyl-β-p-methoxyphenylpropionate.*—Concentrated sulphuric acid (12 g.) was added to a solution of the above propionic acid (30 g.), in absolute ethanol (150 c.c.), and the mixture refluxed for 2½ hours. The product (27 g.) was obtained as a viscous oil suitable for the next stage of the synthesis. In an attempt to obtain a specimen for analysis, the crude ester (0·5 g.) was distilled. A colourless oil, b. p. 195°/1 mm., was obtained which solidified on treatment with ethanol. After recrystallisation from ethanol it was identified as 4-*p*-methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin, m. p. and mixed m. p. 113°.

*Oxime of Ethyl β-2-Keto*cyclo*hexyl-β-p-methoxyphenylpropionate* (I; Ar = C_6H_4·OMe).—Hydroxylamine hydrochloride (9 g.) and anhydrous sodium acetate (18 g.) in a little water were added to a solution of the above crude ester (23 g.) in ethanol, and the mixture refluxed for 5 minutes. After several hours, the *oxime* (22 g.) was collected. It formed colourless needles (from ethanol), m. p. 146° (Found: C, 67·7; H, 7·8; N, 4·5. $C_{18}H_{25}O_4N$ requires C, 67·6; H, 7·8; N, 4·4%).

4-p-*Methoxyphenyl*-1-*ethyldecahydroquinoline.*—The above oxime (10 g.) in ethanol (300 c.c.) was

* *Added, June 29th*, 1948.—After several months this base crystallised spontaneously. It was recrystallised from light petroleum and then formed colourless needles, m. p. 61°.

reduced with hydrogen in the presence of copper chromite (5 g.) at 200° and 165 atmospheres for 3 hours. The acid-soluble fraction was distilled, giving 4-p-*methoxyphenyl*-1-*ethyldecahydroquinoline* (7 g.) as a colourless viscous oil, b. p. 175°/0·3 mm., which solidified on standing. It formed small colourless needles (from ethyl acetate), m. p. 89° (Found: C, 79·0; H, 9·8; N, 5·2. $C_{18}H_{27}ON$ requires C, 79·1; H, 9·9; N, 5·1%).

The *picrate*, prepared in ethanol and recrystallised from glacial acetic acid, formed stout yellow needles, m. p. 182—184° (Found: C, 57·4; H, 6·0. $C_{18}H_{27}ON,C_6H_3O_7N_3$ requires C, 57·3; H, 6·0%).

The *hydrochloride*, prepared by passing dry hydrogen chloride through a solution of the base in ether, formed colourless needles from ethanol–ether, m. p. 248—250° (Found: C, 69·9; H, 8·8. $C_{18}H_{28}ONCl$ requires C, 70·0; H, 9·0%).

4-p-*Hydroxyphenyl*-1-*ethyldecahydroquinoline Hydrobromide*.—Hydrobromic acid (3 c.c.; 48%) was added to a solution of the methoxy-base (1·3 g.) in glacial acetic acid (1·75 c.c.), and the mixture refluxed for 9 hours. On cooling in ice, 4-p-*hydroxyphenyl*-1-*ethyldecahydroquinoline hydrobromide* (1·27 g.) was obtained. It crystallised from glacial acetic acid in small colourless needles, m. p. 227—228° (Found: C, 59·95; H, 7·5; N, 4·3. $C_{17}H_{26}ONBr$ requires C, 60·0; H, 7·6; N, 4·1%). The free base, which was soluble in alkali, gave no colour with ferric chloride.

We thank the Department of Scientific and Industrial Research for a maintenance grant (to T. W.), and Mr. J. M. L. Cameron for the microanalyses. One of us (G. M. B.) has been working with an I.C.I. Research Fellowship.

UNIVERSITY OF GLASGOW. [*Received, January 19th,* 1948.]

---

408. *Reactions of Polynitro-aromatic Compounds with Alkaline Sulphides. Part I. Aryl Monosulphide Formation by Interaction of Sodium Thioaryloxides with Polynitro-aromatic Compounds containing Labile Nitro-groups.*

By HERBERT H. HODGSON and EDWARD R. WARD.

From a study of twenty-three reactions between nitro-thioaryloxides and polynitro-derivatives of benzene, toluene, and naphthalene, it is concluded that aromatic monosulphides are formed *via* the process:

$$R(NO_2)_{x-1}\cdot SNa + R(NO_2)_y = [R(NO_2)_{x-1}]_2S + NaNO_2$$

Only polynitro-compounds with labile nitro-groups react, and, in a few cases involving *p*-dinitro-compounds, the reaction is more complex; *e.g.* a 40% yield of *pp'*-dinitroazobenzene has been obtained from the interaction of *p*-dinitrobenzene with sodium *p*-nitrothiophenoxide, in addition to what is apparently a mixture of monosulphides.

It is tentatively suggested that two distinct reactions are involved in the interactions of polynitro-aromatic compounds with alkaline sulphides, *viz.*, (1) whole or partial reduction of a nitro-group (or groups), and (2) replacement of a nitro-group (or groups) by a sulphur-containing radical, *e.g.* –SNa with sodium sulphides. Aromatic monosulphides then arise by the further reaction cited above. The relative extent of each reaction appears to be largely determined by the positivity of the carbon atom to which the reactive nitro-group is attached.

THE great variety of products which arise during the reduction of nitro-aromatic compounds by alkaline sulphides includes those formed by whole or part reduction of the nitro-group(s), and those formed by replacement of the nitro-group(s) by the anionoid sulphide reagent such as thiols and mono- and di-sulphides; *e.g.*, *o*-dinitrobenzene can give *o*-nitroaniline, *o*-nitrothiophenol, and 2 : 2'-dinitrodiphenyl mono- and di-sulphides [the production of polysulphides (Blanksma, *Rec. Trav. chim.*, 1901, **20**, 144) is regarded by the present authors as doubtful]. 2 : 3 : 5-Trinitro-1 : 4-dimethylbenzene gives 5-nitro-3-amino-1 : 4-dimethylbenzene-2-sulphonic acid with either sodium sulphide or sodium hydrogen sulphide in ethanol (Blanksma, *ibid.*, 1905, **24**, 49).

Reduction of nitro-groups and also their replacement by anionoid reagents are facilitated by the presence of kationoid substituents, particularly when in *op*-positions (Cohen and McCandlish, *J.*, 1905, **87**, 1257; Loudon and Shulman, *J.*, 1941, 722). Hence the positivity of the carbon atom to which the reacting nitro-group is attached is a determining factor of the reactivity, *viz.*, with increase of positivity replacement by –SNa (or other sulphur-containing radicals as in disulphide formation) progressively competes with reduction until it becomes exclusive.

Accumulating experimental evidence (Hodgson and Ward, unpublished work) indicates that monosulphides arise generally *via* a two-stage mechanism, *viz.*, (1) formation of thioaryl oxide and (2) its reaction with unchanged nitro-compound. Since previous work on such reactions between thioaryloxides and nitro-compounds has been almost confined to the anthra-

quinone series (D.R-PP. 116,951, 224,589, 254,561; cf. also Decker and Würsch, *Annalen*, 1906, **348**, 239; Gattermann, *Annalen*, 1912, **393**, 113) with a few isolated examples in the benzene series, it was thought desirable to investigate reactions of this type with a variety of benzene and naphthalene compounds.

In the present paper, the second stage of this mechanism has been demonstrated for reactions between *o*- and *p*-dinitrobenzene, 3 : 4-dinitrotoluene, 3 : 4 : 5-trinitrotoluene, 1 : 2- and 1 : 4-dinitronaphthalenes, and 1 : 4 : 5-trinitronaphthalene with sodium *o*- and *p*-nitro-, 2 : 4-dinitro-, and 2-nitro-4-methyl-thiophenoxide and 2- and 4-nitro- and 2 : 4-dinitro-1-thionaphthoxide. The reaction occurs only with compounds which possess labile nitro-groups.

Whereas no precise quantitative measurements were made, it appeared that sodium 2-nitro-4-methylthiophenoxide was the most reactive reagent, and that sodium *p*-nitro- was more reactive than sodium *o*-nitro-thiophenoxide, though both were more reactive than the corresponding 2 : 4-dinitro-compound. Similarly sodium 2- and 4-nitro-1-thionaphthoxides were more reactive than 2 : 4-dinitro-1-thionaphthoxide, which appears to be the least reactive of all the reagents tried. The above data are in accord with the work of Evans and Smiles (*J.*, 1935, 181), who pointed out that the negative character of the thiol group was weakened by nitro-groups in *op*-positions. Sodium *o*-aminothiophenoxide gave unsatisfactory results in preliminary trials and was not further investigated. The following did not react: nitrobenzene and 1 : 8-dinitronaphthalene with sodium *p*-nitrothiophenoxide, *m*-dinitrobenzene and 1 : 3 : 5-trinitrobenzene with sodium 4-nitro-1-thionaphthoxide, and 1-nitronaphthalene, 1 : 5-dinitronaphthalene, and 2 : 6-dinitronaphthalene with sodium *o*-nitrothiophenoxide. Whilst the reaction between sodium 4-nitro-1-thionaphthoxide and *p*-dinitrobenzene afforded the expected 4-nitrophenyl 4-nitro-1-naphthyl sulphide, the corresponding reaction between sodium *p*-nitrothiophenoxide and 1 : 4-dinitronaphthalene gave a pure dinitrophenyl naphthyl sulphide wh'ch has not yet been identified but differs from the above, and also from 4-nitrophenyl 1-nitro-2-naphthyl sulphide which was a possible reaction product (Hodgson and Leigh, *J.*, 1938, 1031).

The following reactions involving *p*-dinitrobenzene were complex *viz.*, with sodium *o*-nitro- and *p*-nitro-thiophenoxides, and with 2-nitro-1-thionaphthoxide. The product obtained with sodium *o*-nitrothiophenoxide appears to be a mixture of difficultly separable monosulphides, possibly 2 : 4′-dinitro- and 2 : 2′-dinitro-diphenyl sulphides; the latter would be an anomalous result (cf. Hodgson and Leigh, *loc. cit.*). Sodium *p*-nitrothiophenoxide gave a similar mixed product but in addition *ca.* 40% of *pp*′-dinitroazobenzene was obtained, which must have been due to the reduction of *p*-dinitrobenzene by the thiophenoxide although no oxidation products of the latter were isolated (cf. Gattermann, *loc. cit.*, who reported that thio-alkyl and -benzyl-oxides in reaction with nitro-derivatives of anthraquinone were oxidised to disulphides with reduction of the nitro- to the amino-group; cf. also Richardson, *J.*, 1926, 522; Loudon and Holmes, *J.*, 1940, 1521; Simons and Ratner, *J.*, 1944, 421). From sodium 2-nitro-1-thionaphthoxide only a very small amount of a complex dark-coloured product could be isolated.

It would appear that dinitro- and trinitro-aromatic compounds are much more reactive towards sodium thioaryloxides than the corresponding chloronitro- or chlorodinitro-compounds. The reactions involving 3 : 4 : 5-trinitrotoluene and 1 : 4 : 5-trinitronaphthalene were completed almost as soon as the reactants were mixed, while 1 : 2- and 1 : 4-dinitronaphthalenes appear to be more reactive than *o*- and *p*-dinitrobenzenes; 3 : 4-dinitrotoluene is the least reactive as would be expected from the neutralising effect of the electron-repelling methyl on the electron-attracting nitro-group, which then has a diminished effect on the neighbouring 3-nitro-group. *o*-Dinitrobenzene is less reactive than *p*-dinitrobenzene, and in this respect resembles the lower reactivity of *o*-chloronitro- compared with *p*-chloronitro-benzene (cf. Hodgson and Wilson, *J.*, 1925, **127**, 440).

3 : 4 : 5-Trinitrotoluene by reaction with a large excess of sodium *p*-nitrothiophenoxide gave the same product and yield as when equimolecular quantities were used, so that the other nitro-groups were rendered inactive by the replacement of the 3-nitro-group on monosulphide formation.

The monosulphides arising from the interaction of thioaryloxides and nitro-aromatic compounds were identified where possible with authentic specimens of known compounds, or with specimens prepared by interaction of the thioaryloxide with the corresponding chloronitro-aromatic compounds. The following new monosulphides were prepared in this way: 2 : 4-*dinitrophenyl* 4-*nitro*-1-*naphthyl* (from sodium 4-nitro-1-thionaphthoxide and 1-chloro-2 : 4-dinitrobenzene); 2- and 4-*nitrophenyl* 2 : 4-*dinitro*-1-*naphthyl* and 2 : 4 : 4′-*trinitro*-1 : 1′-*dinaphthyl* (from sodium *o*- and *p*-nitrothiophenoxide and 4-nitro-1-thionaphthoxide with

1-chloro-2 : 4-dinitronaphthalene); 2 : 6 : 2′-*trinitro*-4-*methyldiphenyl* (from sodium *p*-nitrothiophenoxide and 4-chloro-3 : 5-dinitrotoluene) and 4-*nitrophenyl* 4 : 5-*dinitro*-1-*naphthyl sulphide* (from sodium *p*-nitrophenoxide and 1-bromo-4 : 5-dinitronaphthalene).

The product from sodium *o*-nitrothiophenoxide and 3 : 4-dinitrotoluene was not identical with 2 : 2′-dinitro-4-methyldiphenyl sulphide (from sodium 2-nitro-4-methylthiophenoxide and *o*-dinitrobenzene) and hence must be 2 : 6′-*dinitro*-3′-*methyldiphenyl sulphide*. Similarly that from sodium 2-nitro-4-methylthiophenoxide and 3 : 4-dinitrotoluene must be 2 : 6′-*dinitro*-4 : 3′-*dimethyldiphenyl sulphide*, the 3-nitro-group being labile as above. The product from sodium *p*-nitrothiophenoxide and 3 : 4 : 5-trinitrotoluene was not identical with that obtained from 4-chloro-3 : 5-dinitrotoluene and the same thioaryloxide, and hence must be 2 : 3 : 4′-*trinitro*-5-*methyldiphenyl sulphide*. The product from sodium *p*-nitrothiophenoxide and 1 : 4 : 5-trinitronaphthalene was not identical with 4-nitrophenyl 4 : 5-dinitro-1-naphthyl sulphide (from sodium *p*-nitrothiophenoxide and 1-bromo-4 : 5-dinitronaphthalene) and hence must be 4-nitrophenyl 4 : 8-dinitro-1-naphthyl sulphide.

The work of Zincke and Röse (*Annalen*, 1914, **406**, 108) on the interaction of sodium disulphide with 4-chloro-3-nitrotoluene has been repeated and confirmed; similarly that of Talen (*Rec. Trav. chim.*, 1928, **47**, 782) on the interaction of sodium mono- and di-sulphides with 1-chloro-2 : 4-dinitronaphthalene. Sodium 2-nitro-4-methylthiophenoxide and 2 : 4-dinitro-1-thionaphthoxide have been prepared by reduction of the corresponding disulphides.

1-Chloro-2 : 4-dinitronaphthalene can be satisfactorily prepared directly from 2 : 4-dinitrotoluene-*p*-sulphon-1-naphthalide, utilising the combined hydrolysis-diazotisation procedure of Hodgson and Birtwell (*J.*, 1943, 433), and carrying out the Sandmeyer reaction with the solution obtained in this manner.

Experimental.

(M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.)

Preparation of Initial Materials.—*1-Chloro-2 : 4-dinitronaphthalene.* This was prepared directly in 65% yield from 2 : 4-dinitrotoluene-*p*-sulphon-1-naphthalide by combined hydrolysis, diazotisation, and Sandmeyer reaction (cf. Hodgson and Walker, *J.*, 1933, 1620; Hodgson and Birtwell, *loc. cit.*)

Sodium thioaryloxides. The corresponding aryl disulphide was reduced either in aqueous alcohol with sodium monosulphide–sodium hydroxide, or in ethanol with glucose–sodium hydroxide; after reduction the solution was diluted and the thiol precipitated with hydrochloric acid, filtered off, washed with water, and redissolved in hot ethanol containing *ca.* 1·5 equivs. of sodium hydroxide.

2 : 2′-Dinitro-4 : 4′-dimethyl-1 : 1′-diphenyl disulphide. A solution of 4-chloro-3-nitrotoluene (5 g.) in ethanol (20 c.c.) was refluxed for 90 minutes with one of crystallised sodium sulphide (3·5 g.) and sulphur (0·45 g.) in ethanol (10 c.c.) and water (5 c.c.); the initial intense red colour had then almost disappeared; the mixture was then cooled and the yellow crystalline disulphide (1·8 g.) removed, washed with cold ethanol and water, and dried; m. p. 176°, which was unchanged after one crystallisation from glacial acetic acid (Zincke and Röse, *Annalen*, 1914, **406**, 108, give m. p. 176°).

2-Nitro-4-methylphenylthiol. A suspension of the above disulphide (1 g.) in boiling ethanol (20 c.c.) and water (5 c.c.) containing glucose (0·55 g.) and sodium hydroxide (0·4 g.) was refluxed for 10 minutes; the mixture was then diluted with water (5 vols.) and the thiol precipitated by addition of hydrochloric acid and then removed, washed with water, and redissolved in ethanol (25 c.c.) and water (5 c.c.) containing sodium hydroxide (0·2 g.).

2 : 4 : 2′ : 4′-Tetranitro-1 : 1′-dinaphthyl mono- and di-sulphides. (*a*) A solution of 1-chloro-2 : 4-dinitronaphthalene (2 g.) in acetone (80 c.c.) was treated gradually with a hot solution of sodium sulphide (1 g.) in ethanol (10 c.c.) and water (2 c.c.); the initial red colour, which tended to disappear in a few seconds, became permanent when all the sulphide had been added, and the pure 2 : 4 : 2′ : 4′-tetranitro-1 : 1′-dinaphthyl sulphide (1·4 g.; 75% yield) separated. This, when crystallised from glacial acetic acid, had m. p. 283—284° (Talen, *loc. cit.*, gives m. p. 283°). The filtrate on oxidation with potassium ferricyanide afforded 2 : 4 : 2′ : 4′-tetranitro-1 : 1′-dinaphthyl disulphide (0·35 g.; *ca.* 20% yield).

(*b*) When the chlorodinitronaphthalene [see (*a*) above] (2 g.) was treated with a hot solution of sodium sulphide (0·95 g.) and sulphur (0·15 g.) (corresponding to 0·5 mol. sodium disulphide) in ethanol (10 c.c.) and water (4 c.c.), a precipitate of monosulphide (1·6 g.; m. p. 275—280°) resulted; the disulphide (0·35 g.) was obtained by oxidation of the filtrate as under (*a*).

(*c*) When 1 mol. of sodium sulphide was used, the reaction product remained in solution, and on oxidation with potassium ferricyanide, afforded the disulphide (1·95 g.; *ca.* 100% yield), which when recrystallised from glacial acetic acid had m. p. 216—220° (decomp.) [Talen, *loc. cit.*, gives 230° (decomp.)].

Preparation of Aryl Monosulphides by the Reaction of Sodium Thioaryloxides with Halogenonitroaromatic Compounds.—General procedure. A solution of the halogeno-compound (*ca.* 30—50% excess) in hot ethanol was treated with a hot solution of the thioaryloxide in aqueous ethanol; in some cases reaction was immediate and the monosulphide separated from the hot solution, but otherwise the separation only occurred after refluxing the mixture, and an indication of the completion of the reaction was then given by the depth of colour of the solution. The monosulphide was removed, washed with water and ethanol, dried, and crystallised from a suitable solvent (usually aqueous or glacial acetic acid).

2 : 4′-Dinitrodiphenyl sulphide. *p*-Chloronitrobenzene (2·5 g.) in ethanol (20 c.c.) and sodium *o*-nitrothiophenoxide (*ca.* 2·3 g.) were heated together under reflux for 4 hours (yield 1·8 g.). When crystallised from glacial acetic acid the sulphide had m. p. 162°, and mixed melt with the product from the interaction of *o*-dinitrobenzene with sodium *p*-nitrothiophenoxide, 163—164° (Evans and Smiles, *J.*, 1935, 185,

TABLE OF RESULTS.

No.	Thioaryloxide.	Polynitro-aromatic compound.	Reaction period (mins.).	Yield (%). Crude.	Yield (%). Pure.	Product.	Remarks.
1	*o*-Nitrothiophenoxide	*o*-Dinitrobenzene	45	—	56	2 : 2-Dinitrodiphenyl sulphide, m. p. 122° (ethanol).	—
2	*o*-Nitrothiophenoxide	3 : 4-Dinitrotoluene	45	—	—	2 : 6′-*Dinitro*-3′-*methyldiphenyl sulphide*, m.p. 98° (50% aqueous acetic acid) (Found : S, 10·67. $C_{13}H_{10}O_4N_2S$ requires S, 11·07%).	Product separates as an oil, readily soluble in hot ethanol.
3	*o*-Nitrothiophenoxide	1 : 2-Dinitronaphthalene	30	71	—	2-Nitrophenyl 2-nitro-1-naphthyl sulphide m. p. 195—197° (glacial acetic acid) (Hodgson and Leigh, *J.*, 1938, 1031, give 196—197°).	—
4	*o*-Nitrothiophenoxide	1 : 4-Dinitronaphthalene	30	69	—	2-Nitrophenyl 4-nitro-1-naphthyl sulphide m. p. 159—160° (glacial acetic acid) (*idem*, *ibid.*, give 157—158°).	—
5	*p*-Nitrothiophenoxide	*o*-Dinitrobenzene	30	—	73	2 : 4′-Dinitrophenyl sulphide (glacial acetic acid), m. p. 163—164°.	
6	*p*-Nitrothiophenoxide	3 : 4 : 5-Trinitrotoluene	10	—	95	2 : 3 : 4′-*Trinitro*-5-*methyldiphenyl sulphide*, m. p. 155—156° (alcohol) (Found : S, 9·22. $C_{13}H_9O_6N_3S$ requires S, 9·5%).	Cream-coloured needles.
7	*p*-Nitrothiophenoxide	1 : 2-Dinitronaphthalene	30	79	—	4-Nitrophenyl 2-nitro-1-naphthyl sulphide, m. p. 121—122° (50% aqueous acetic acid) (Hodgson and Leigh, *J.*, 1938, 1031, give 121—122°).	—
8	*p*-Nitrothiophenoxide	1 : 4 : 5-Trinitronaphthalene	10	—	—	4-*Nitrophenyl* 4 : 8-*dinitro*-1-*naphthyl sulphide* (glacial acetic acid), m. p. 216—217° (Found : S, 8·9. $C_{16}H_9O_6N_3S$ requires S, 8·6%).	Sand-coloured parallelepipeds.
9	2-Nitro-4-methylthiophenoxide	*o*-Dinitrobenzene	5	—	80	2 : 2′-*Dinitro*-4-*methyldiphenyl sulphide*, m. p. 127—128° (50% aqueous acetic acid) Found : S, 11·1. $C_{13}H_{10}O_4N_2S$ requires S, 11·1%).	Lemon-yellow needles.
10	2-Nitro-4-methylthiophenoxide	3 : 4-Dinitrotoluene	90	—	75	2 : 6′-*Dinitro*-4 : 3′-*dimethyldiphenyl sulphide*, m. p. 131—132° (50% aqueous acetic acid) (Found : S, 10·35. $C_{14}H_{12}O_4N_2S$ requires S, 10·56%).	Pale yellow elongated plates.
11	2 : 4-Dinitrothiophenoxide	*o*-Dinitrobenzene	90	—	20	2 : 4 : 2′-Trinitrodiphenyl sulphide, m. p. 107° (50% aqueous acetic acid).	—
12	2 : 4-Dinitrothiophenoxide	*p*-Dinitrobenzene	90	—	30	2 : 4 : 4′-Trinitrodiphenyl sulphide, m. p. 168° (50% aqueous acetic acid).	—

13	2 : 4-Dinitrothiophen-oxide	1 : 4-Dinitronaphth-alene	90	—	45	2 : 4-Dinitrophenyl 4-nitro-1-naphthyl sulphide, m. p. 185—190° (75% aqueous acetic acid).	—	—
14	2-Nitro-1-thionaphth-oxide	*o*-Dinitrobenzene	30	—	63	2-Nitrophenyl 2-nitro-1-naphthyl sulphide, m. p. 193—196° (glacial acetic acid) (Hodgson and Leigh, *J.*, 1938, 1031 give 196—197°).	—	—
15	2-Nitro-1-thionaphth-oxide	1 : 2-Dinitronaphth-alene	30	50	—	2 : 2′-Dinitro-1 : 1′-dinaphthyl sulphide, m. p. 204° (glacial acetic acid) (Hodgson and Leigh, *J.*, 1937, 1352, give 204—205°).	—	—
16	2-Nitro-1-thionaphth-oxide	1 : 4-Dinitronaphth-alene	30	41	—	2 : 4′-Dinitro-1 : 1′-dinaphthyl sulphide, m. p. 162—163° (glacial acetic acid) (Hodgson and Leigh, *J.*, 1937, 1352, give 162—163°).	—	—
17	4-Nitro-1-thionaphth-oxide	*o*-Dinitrobenzene	30	54	—	2-Nitrophenyl 4-nitro-1-naphthyl sulphide, m. p. 157—158° (glacial acetic acid) (Hodgson and Leigh, *J.*, 1938, 1031, give 157—158°).	—	—
18	4-Nitro-1-thionaphth-oxide	*p*-Dinitrobenzene	30	36	—	4-Nitrophenyl 4-nitro-1-naphthyl sulphide, m. p. 232—236° (glacial acetic acid) (Hodgson and Leigh, *J.*, 1938, 1031, give 236—238°).	—	—
19	4-Nitro-1-thionaphth-oxide	1 : 2-Dinitronaphth-alene	30	—	55	2 : 4′-Dinitro-1 : 1′-dinaphthyl sulphide, m. p. 163—164° (glacial acetic acid, twice) (Hodgson and Leigh, *J.*, 1938, 1032, give 162—163°).	—	—
20	4-Nitro-1-thionaphth-oxide	1 : 4-Dinitronaphth-alene	30	64	—	4 : 4′-Dinitro-1 : 1′-dinaphthyl sulphide, m. p. 237—240° (glacial acetic acid) (Hodgson and Leigh, *J.*, 1937, 1352, give 239—240°).	—	—
21	2 : 4-Dinitrothio-naphthoxide	*o*-Dinitrobenzene	90	—	Very small	2-Nitrophenyl 2 : 4-dinitro-1-naphthyl sulphide, m. p. 220—228° (glacial acetic acid).	—	—
22	2 : 4-Dinitrothio-naphthoxide	*p*-Dinitrobenzene	90	*ca.* 5	—	4-Nitrophenyl 2 : 4-dinitro-1-naphthyl sulphide, m. p. 180—200°.	Product somewhat impure even after two crystallisations.	—
23	2 : 4-Dinitrothio-naphthoxide	1 : 4-Dinitronaphth-alene	180	*ca.* 10	—	2 : 4 : 4′-Trinitro-1 : 1′-dinaphthyl sulphide, m. p. 208—210° (glacial acetic acid) (Found: S, 7·7. $C_{20}H_{11}O_6N_3S$ requires S, 7·63%).	—	—

give m. p. 158—159°) (Found : S, 11·72. Calc. for $C_{12}H_8O_4N_2S$: S, 11·6%). In contrast, the reaction between *o*-chloronitrobenzene and sodium *p*-nitrothiophenoxide was much slower than the above; 45% of unchanged *o*-chloronitrobenzene was recovered by steam distillation after 6 hours' heating under reflux, and the reaction product itself was difficult to purify (Found : S, 10·95%).

2 : 4 : 4′-*Trinitrodiphenyl sulphide.* This compound was prepared from 1-chloro-2 : 4-dinitrobenzene (5 g.), ethanol (50 c.c.), and sodium *p*-nitrothiophenoxide (2·5 g.). The reaction was immediate, and the yield of monosulphide almost quantitative; it separated from 80% aqueous acetic acid in lemon-yellow plates, m. p. 164° and mixed m. p. 165° with the same product from the reaction of *p*-dinitrobenzene with sodium 2 : 4-dinitrothiophenoxide (Blanksma, *Rec. Trav. chim.*, 1901, **20**, 405, gives m. p. 155°) (Found : S, 10·1. Calc. for $C_{12}H_7O_6N_3S$: S, 10·0%).

2 : 4 : 2′-*Trinitrodiphenyl sulphide.* When this compound was prepared from sodium *o*-nitrothiophenoxide, 2 hours' heating under the reflux was required for the completion of the reaction. The yield was almost quantitative. The sulphide was crystallised from 80% aqueous acetic acid from which it separated in lemon-yellow plates, m. p. 116° which could not be raised by further crystallisation (Blanksma, *loc. cit.*, gives m. p. 131°) (Found : S, 9·62. Calc. for $C_{12}H_7O_6N_3S$: S, 10·0%).

2 : 4-*Dinitrophenyl* 4-*nitro*-1-*naphthyl sulphide.* This separated at once when 1-chloro-2 : 4-dinitrobenzene reacted with sodium 4-nitro-1-thionaphthoxide. The *sulphide* crystallised from 80% aqueous acetic acid in cream micro-needles, m. p. 193° (Found : S, 8·31. $C_{16}H_9O_6N_3S$ requires S, 8·63%).

4-*Nitrophenyl* 2 : 4-*dinitro*-1-*naphthyl sulphide.* The *sulphide* (2·5 g.) separated immediately when 1-chloro-2 : 4-dinitronaphthalene (2·5 g.) reacted with sodium *p*-nitrothiophenoxide (1·5 g.); it crystallised from hot 80% aqueous acetic acid in sand-coloured rhombs, m. p. 197—198° (Found : S, 8·16. $C_{16}H_9O_6N_3S$ requires S, 8·63%).

2-*Nitrophenyl* 2 : 4-*dinitro*-1-*naphthyl sulphide.* This was prepared as above from the *o*-nitro-compound. After 10 minutes' heating under reflux separation was complete. The *sulphide* (2·5 g.) crystallised from 80% aqueous acetic acid in ochre hexagonal plates, m. p. 225—226° (Found : S, 8·67. $C_{16}H_9O_6N_3S$ requires S, 8·63%).

2 : 4 : 4′-*Trinitro*-1 : 1′-*dinaphthyl sulphide.* 4-Nitro-1-thionaphthoxide similarly gave the *dinaphthyl sulphide* which crystallised from glacial acetic acid in cream micro-needles, m. p. 216° (Found : S, 7·9. $C_{20}H_{11}O_6N_3S$ requires S, 7·63%).

Reactions with 4-*chloro*-3-*nitrotoluene.* The yields of monosulphide were negligible when 4-chloro-3-nitrotoluene reacted with sodium 2-nitro- and 2-nitro-4-methyl-thiophenoxide and 4-nitro-1-thionaphthoxide, even if reaction was allowed to proceed for 8 hours under reflux and although the thioaryloxide had disappeared.

2 : 6 : 2′-*Trinitro*-4-*methyldiphenyl sulphide.* When a mixture of 4-chloro-3 : 5-dinitrotoluene (2 g.) in ethanol (30 c.c.) was refluxed for 5½ hours with sodium *p*-nitrothiophenoxide (1·75 g.) the *diphenyl sulphide* was formed; it separated (1·5 g.) from 80% aqueous acetic acid in lemon-yellow needles, m. p. 100° (Found : S, 9·52. $C_{13}H_9O_6N_3S$ requires S, 9·52%), which were readily soluble in cold acetic acid.

4-*Nitrophenyl* 4 : 5-*dinitro*-1-*naphthyl sulphide.* This was prepared by refluxing 1-bromo-4 : 5-naphthalene (0·75 g.) in acetone (60 c.c.) with sodium *p*-nitrothiophenoxide (0·5 g.) for 10 minutes; it separated from the hot solution in almost quantitative yield and crystallised from glacial acetic acid in lemon-yellow crystals of the *sulphide*, m. p. 221° (Found : S, 8·59. $C_{16}H_9O_6N_3S$ requires S, 8·6%).

Preparation of Aryl Monosulphides by the Reaction of Sodium Thioaryloxides with Dinitro-aromatic Compounds.—General procedure. A hot solution of the dinitro-aromatic compound (0·0075 mol.) in the minimum amount of ethanol was treated with a hot solution of the thioaryloxide (0·005 mol.) in 80—90% aqueous ethanol containing *ca.* 1·5 equivs. of sodium hydroxide. In several cases reaction was completed almost at once, but, generally, heating under reflux was necessary until the red colour due to the sodium thioaryloxide had disappeared. The monosulphide usually separated from the hot solution. After removal, it was washed with cold alcohol and water, and dried before recrystallisation. Some of the reaction products were dark owing to the presence of impurities. These dark products were often accompanied by some sulphur. A few of the nitro-compounds were relatively insoluble in hot alcohol (*e.g.* 1 : 4 : 5-trinitronaphthalene, 2 : 6-dinitronaphthalene), and a suspension in this medium was used.

Some Abnormal Reactions involving p-*Dinitro-aromatic Compounds.*—(*a*) Sodium *o*-nitrothiophenoxide (1·75 g.) and *p*-dinitrobenzene (2 g.) were treated as above and, after refluxing for 30 minutes, the cooled mixture was filtered. The yellow crystalline product (1 g.; *ca.* 40% yield calculated as monosulphide) was treated with steam to remove any unchanged *p*-dinitrobenzene; the crude product had m. p. 138—140° which was raised to 142—145° by repeated crystallisation from glacial acetic acid (Found : N, 11·7; S, 11·0. Calc. for $C_{12}H_8O_4N_2S$: N, 10·0; S, 11·6%).

(*b*) Sodium *p*-nitrothiophenoxide (4·0 g.) and *p*-dinitrobenzene (4·0 g.) were treated as above, and the reddish-orange product (3·1 g.) dissolved in the minimum amount of boiling glacial acetic acid, from which *pp*′-dinitroazobenzene (1·3 g.) separated on cooling and was filtered off; m. p. 223° (Found : N, 20·4. Calc. for $C_{12}H_8O_4N_4$: N, 20·6%). From the filtrate, on concentration, an orange-yellow product (1·1 g.) separated, m. p. 147—148° after extraction with a little boiling glacial acetic acid (Found : S, 10·5. Calc. for $C_{12}H_8O_4N_2S$: S, 11·5%). The m. p. was not raised by treatment with a hot aqueous alcoholic solution of sodium hydroxide and glucose, although some thioaryloxide was produced as indicated by oxidation of the intense blue liquor with hot potassium ferricyanide solution. The original filtrate, after removal of the reaction product, contained some unchanged starting materials. *p*-Dinitrobenzene was removed by steam distillation; a substance of low m. p. remained which was soluble in hot ethanol but not in alkali hydroxides. The steam distillate, after removal of *p*-dinitrobenzene, gave no precipitate on addition of barium chloride, indicating the absence of sodium *p*-nitrobenzenesulphonate.

(*c*) Sodium 2-nitro-1-thionaphthoxide (1·0 g.) and *p*-dinitrobenzene (1·0 g.), after refluxing for 30 minutes as above, afforded only a black product (0·2 g.) which on crystallisation from glacial acetic acid had m. p. 223—227°; the solution in acetic acid was purple and changed through the colour sequence blue-green, green, and lilac on dilution with water, these colours being reversed on addition of increasing amounts of glacial acetic acid to the lilac solution.

(*d*) Sodium *p*-nitrothiophenoxide (1·25 g.) and 1 : 4-dinitronaphthalene (1·5 g.), after refluxing for 30

minutes as above, afforded a crystalline product (1·75 g.; 76% yield calculated as monosulphide) which was removed from the hot solution and separated from hot glacial acetic acid in lemon-yellow crystals, m. p. 152—153° (Found : S, 9·91. Calc. for $C_{16}H_{10}O_4N_2S$: S, 9·8%).

The authors thank Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals, the Department of Scientific and Industrial Research for a Senior Research Award to one of them (E. R. W.), and Mr. G. Walker for the preparation of several initial materials.

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, January 26th,* 1948.]

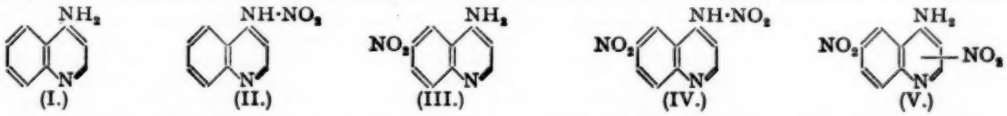
---

409. *The Nitration of 4-Aminoquinoline.*

By J. C. E. SIMPSON and P. H. WRIGHT.

The nitration of 4-aminoquinoline is stated (Tschitschibabin *et al.*, *Ber.*, 1925, **58**, 803) to yield (III) by isomerisation of the nitroamine (II). Re-examination of the reaction has now shown that (III) undergoes further nitration to (IV); the dinitroaminoquinoline (V) formed by isomerisation of (IV) is probably 3 : 6-*dinitro*-4-*aminoquinoline*.

THE nitration of 4-aminoquinoline, first studied by Claus and Frobenius (*J. pr. Chem.*, 1897, **56**, 202), was later examined by Tschitschibabin, Witkowsky, and Lapschin (*Ber.*, 1925, **58**, 803), who stated that the course of the reaction is represented by the stages (I) ⟶ (II) ⟶ (III).



(I.) (II.) (III.) (IV.) (V.)

As the reaction seemed to offer a ready means of preparing (III), we repeated the work of Tschitschibabin *et al.* (*loc. cit.*), but were unable to isolate (III) by any simple procedure. Furthermore, although the Russian authors claimed to have established the orientation of (III), for which they record m. p. 272°, by oxidation to 5-nitroanthranilic acid, we found (this vol., p. 1707) that 6-nitro-4-aminoquinoline, prepared from 4-chloro-6-nitroquinoline, has m. p. 312°.

We have therefore examined the reaction in some detail. A complex mixture seems to be formed, and, although a complete separation of the products was not possible, we were able to isolate (III) after prolonged fractionation, and have also established that the sequence (III) ⟶ (IV) ⟶ (V) occurs during the reaction. This conclusion was reached in the following way.

The crude nitration product, free from any unisomerised nitroamine (II or IV), could not be resolved by crystallisation, and was therefore acetylated. It was thus separated into a crystalline amphoteric product, m. p. 282—283°, which gave analytical figures in agreement with the formula $C_9H_6O_4N_4$, and a non-crystalline mixture of acetamido-compounds. The molecular formula of the substance, m. p. 282—283°, is that of a dinitroaminoquinoline, and confirmation of this was obtained by nitrating 6-nitro-4-aminoquinoline. When the reaction was carried out under conditions similar to those used for 4-aminoquinoline, the acidic 6-*nitro*-4-*nitroaminoquinoline* (IV) was isolated in high yield, and this compound was readily isomerised in acid solution to a 6 : *x*-dinitro-4-aminoquinoline (V), identical with the compound, m. p. 282—283°. We have not obtained formal proof of the orientation of this amine, but the contrast between its properties (amphoteric character, resistance to acetylation) and those shown by other nitroaminoquinolines, and the fact that 4 : 6-diamino- and 4-amino-6-acetamido-quinaldine are nitrated in the 3-position (G.P. 613,065), suggest that it is 3 : 6-*dinitro*-4-*aminoquinoline*.

When (V) was treated with 5N-hydrochloric acid under reflux, it was partly hydrolysed to an acidic compound, m. p. 354° (decomp.), of formula $C_9H_5O_5N_3$, which—if its precursor has been correctly designated—is therefore 3 : 6-*dinitro*-4-*hydroxyquinoline*. This compound was also produced, together with a mixture of bases, by acid hydrolysis of the non-crystalline acetamido-compounds (see above). The mixed bases could not be separated by crystallisation, but fractional extraction with dilute acetic acid, followed by conversion into the hydrochlorides, yielded 6-nitro-4-aminoquinoline (III), identical with the compound prepared from 4-chloro-6-nitroquinoline (Simpson and Wright, *loc. cit.*).

EXPERIMENTAL.

(Melting points are uncorrected.)

Nitration of 4-Aminoquinoline.—Nitric acid (5·6 c.c., *d* 1·40) was added during 35 minutes to a stirred solution of 4-aminoquinoline (10 g.) in concentrated sulphuric acid (55 c.c.) at −7° to + 2°. The clear

solution was kept at 8° until no acid-insoluble material was obtained on dilution of a sample (1 hour); it was then poured on ice (250 g.), and the mixture basified with 20% aqueous sodium hydroxide. The solid (A) was collected, washed, and dried in a desiccator (12·1 g.); it had m. p. 250—270° (decomp.), and on repeated crystallisation gave, in poor yield, pale yellow needles, m. p. 278—281° alone and when mixed with the dinitroaminoquinoline (see below).

3(?) : 6-*Dinitro*-4-*aminoquinoline*.—The solid (A) (20 g.) was refluxed for ½ hour with acetic anhydride (60 c.c.), and the solution was left in an evacuated desiccator over sodium hydroxide for 24 hours. The solid (B) which had separated was collected (12 g.), and solvent removed from the filtrate, giving a dark brown resin (C). Continued recrystallisation of (B) from ethyl acetate and finally from aqueous acetone gave, with heavy losses, 3(?) : 6-*dinitro*-4-*aminoquinoline* as pale yellow needles, m. p. 282—283° (Found : C, 46·5; H, 2·7; N, 24·0. $C_9H_6O_4N_4$ requires C, 46·15; H, 2·6; N, 23·9%), virtually insoluble in water and in cold dilute ammonium hydroxide, but appreciably soluble in hot dilute hydrochloric acid and in hot dilute sodium hydroxide; as anticipated from its method of isolation, the compound was unaffected by boiling acetic anhydride.

3(?) : 6-*Dinitro*-4-*hydroxyquinoline*.—The resin (C) was refluxed for 35 minutes with 2N-hydrochloric acid, filtered hot (solid D), cooled, and again filtered (solid E); the filtrate was basified with ammonia, and the solid (F) collected. The solid (D) (0·9 g.) was practically insoluble in the common solvents, and was best purified by repeated dissolution in very dilute ammonium hydroxide and reprecipitation with acetic acid; in this way 3(?) : 6-*dinitro*-4-*hydroxyquinoline* was obtained as colourless needles, m. p. 352—354° (decomp.) (Found : C, 46·1; H, 2·2; N, 17·55. $C_9H_5O_5N_3$ requires C, 46·0; H, 2·1; N, 17·9%), which had no basic properties. Similar treatment of (E) (1 g.) gave a product, m. p. 312—316° (decomp.), which was extracted with hot acetic acid; the insoluble portion, after treatment with dilute ammonia and precipitation with acetic acid, had m. p. 347° (decomp.) alone and mixed with 3(?) : 6-dinitro-4-hydroxyquinoline. The same compound, m. p. and mixed m. p. 348—350° (decomp.), was obtained (30—40%) by refluxing 3(?) : 6-dinitro-4-aminoquinoline for 3 hours with 5N-hydrochloric acid (100 parts); the reaction was very slow, and at least 50% of unchanged amine (from which more hydroxy-compound was obtainable by renewed hydrolysis) was recoverable from the filtrate.

6-*Nitro*-4-*aminoquinoline*.—The solid (F) (6 g.) was extracted with 15-c.c. portions of cold 1% aqueous acetic acid until no further material was removed (13 extractions; total solids extracted = 4 g.). The material obtained by basifying the first 9 extracts was recrystallised several times from hot 2N-hydrochloric acid and then basified, yielding 6-nitro-4-aminoquinoline as an orange solid, m. p. 303—306° (decomp.), not depressed by admixture with a sample [m. p. 311—312° (decomp.)] prepared from 4-chloro-6-nitroquinoline (Simpson and Wright, *loc. cit.*); the corresponding acetyl derivative had m. p. 228—229° alone and mixed with authentic material (m. p. 228—229°; *loc. cit.*).

6-*Nitro*-4-*nitroaminoquinoline*.—Concentrated nitric acid (0·4 c.c., *d* 1·40) was added during 2 minutes to a stirred solution of 6-nitro-4-aminoquinoline (0·5 g.) in concentrated sulphuric acid (4 c.c.) at −16° to −20°. The solution was immediately poured on ice (50 g.), and the suspension made alkaline at 0° with ammonium hydroxide. The solution was filtered from a trace of insoluble material, acidified (hydrochloric acid), and the crude 6-*nitro*-4-*nitroaminoquinoline* (0·5 g.) recrystallised from aqueous acetone, from which it formed orange-yellow prismatic needles, insoluble in ether and ligroin, which decomposed at 216° without melting (Found : C, 45·6; H, 3·0; N, 23·95. $C_9H_6O_4N_4$ requires C, 46·15; H, 2·6; N, 23·9%). When it (0·2 g.) was added during 8 minutes to stirred concentrated sulphuric acid (5 c.c.) at 0—5°, a clear solution was formed, which was poured on ice (50 g.) and filtered from traces of insoluble matter. Basification and crystallisation from aqueous acetone gave yellow needles (0·13 g.) of 3(?) : 6-dinitro-4-aminoquinoline, m. p. 281—283° alone and mixed with the sample already described.

WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY,
LIVERPOOL SCHOOL OF TROPICAL MEDICINE.

[*Received, January 30th,* 1948.]

410. *Some* Bz-*Substituted*-3-*nitroquinolines*.

By J. S. MORLEY and J. C. E. SIMPSON.

3-Nitroquinolines are readily prepared by refluxing compounds of type (I) in acetic acid with an arylamine hydrochloride. The method has been successfully applied to compounds (I) obtained from aniline and the three toluidines, but fails with *p*-nitroaniline and with 2-nitro-*p*-toluidine.

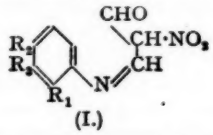
The effect of using the salt of an arylamine different from that used in the preparation of (I) has been studied, and the results are discussed in terms of the hypothesis that the ring-closure occurs *via* (VII) by loss of a proton and arylamine.

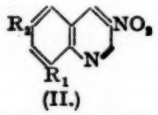
THE methods to be found in the literature for the synthesis of 3-nitroquinolines do not offer attractive routes for the preparation of *Bz*-substituted homologues or analogues. Clemo and Swan (*J.*, 1945, 867) obtained 3-nitro-6 : 7-dimethoxy- and -methylenedioxy-quinoline by extending the methazonic acid–*o*-aminobenzaldehyde reaction (D.R.-P. 335,197), and 3-nitro-4-hydroxy- and thence * 4-chloro-3-nitro-quinoline have recently been prepared from anthranilic

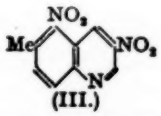
* A compound having markedly different properties has also been described as 4-chloro-3-nitroquinoline by Gouley, Moersch, and Mosher (*J. Amer. Chem. Soc.*, 1947, **69**, 303), who prepared it by nitrating 4-hydroxyquinoline and chlorinating the product. Dr. K. Schofield informs us (private communication) that the compound of Gouley *et al.* is in reality 4-chloro-6-nitroquinoline; we have confirmed this, and have also found that the nitration produces small amounts of 8-nitro-4-hydroxyquinoline.

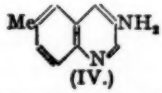
acid and methazonic acid (Bachman, Welton, Jenkins, and Christian, *J. Amer. Chem. Soc.*, 1947, **69**, 365), but the scope of this method, when aldehydes are used, is restricted by the fact that relatively few *o*-aminoaldehydes are known, and the preparation of new analogues would not be likely to be always a simple problem. The method recently published by Uhle and Jacobs (*J. Org. Chem.*, 1945, **10**, 76), involving condensation of nitromalonic aldehyde with an arylamine and cyclisation of the Schiff base in presence of zinc chloride at 200—300°, works well with 2-naphthylamine, but gives only a poor yield when applied to aniline. Colonna (*Chem. Abs.*, 1943, **37**, 3096) has found that 3-nitroquinoline-4-carboxylic acid is a product of the condensation of isatin with nitromethane, but this observation, although suggesting a synthesis of, possibly, general utility, has not been extended to substituted isatins.

The cyclisation of the anils of β-keto-aldehydes to quinoline derivatives has been shown by Petrow (*J.*, 1942, 693) to be greatly facilitated by the addition of a molecular proportion of the hydrochloride of the arylamine, and it seemed likely, in view of the formal similarity between such cyclisations and the reaction of Uhle and Jacobs, that an improvement of the latter might likewise result from the addition of arylamine hydrochloride. Some experiments on these lines have shown that this is in fact the case; 3-nitroquinoline derivatives are formed, sometimes in high yield, simply by refluxing the appropriate anil and arylamine hydrochloride for some hours in acetic acid without the addition of zinc chloride or other condensing agent. Thus 2-nitro-2-formylethylideneaniline (I; $R_1 = R_2 = R_3 = H$) and aniline hydrochloride gave 3-nitroquinoline (II; $R_1 = R_2 = H$) in 41% yield (Uhle and Jacobs, *loc. cit.*, report a 21%


(I.)


(II.)


(III.)


(IV.)

yield); in an experiment in which the hydrochloride was largely replaced by the free base, no quinoline derivative could be isolated. 2-Nitro-2-formylethylidene-*p*-toluidine (I; $R_1 = R_3 = H$, $R_2 = Me$) and *p*-toluidine hydrochloride gave 3-*nitro*-6-*methylquinoline* (II; $R_1 = H$, $R_2 = Me$) in 77% yield (cyclisation of the Schiff base alone by means of zinc chloride gave only a 17% yield), which on nitration gave in high yield a single product, regarded as 3 : 5-*dinitro*-6-*methylquinoline* (III), and on reduction yielded 3-*amino*-6-*methylquinoline* (IV). Similarly, 2-*nitro*-2-*formylethylidene*-m-*toluidine* (I; $R_1 = R_2 = H$, $R_3 = Me$) and *m*-toluidine hydrochloride gave 3-*nitro*-5-(or 7-)*methylquinoline* (55%); the *o*-toluidine *isomer* (I; $R_1 = Me$, $R_2 = R_3 = H$) also reacted with *o*-toluidine hydrochloride, but the yield of 3-*nitro*-8-*methylquinoline* (II; $R_1 = Me$, $R_2 = H$) was low (6·5%). No quinoline derivative was obtained from 2 : 3′-*dinitro*-2-*formylethylidene*-p-*toluidine* (I; $R_1 = H$, $R_2 = Me$, $R_3 = NO_2$) either by fusion with zinc chloride or by refluxing it with the corresponding arylamine hydrochloride in 80% acetic acid.

These results suggested that the ring-closures might occur by acid-induced intramolecular cyclisation of the anils (V) [or (VI)] formed from the arylamine and the Schiff bases, and it

(V). Ar·N:CH·CH(NO_2)·CH:NHAr′ Ar·N:CH·C(NO_2):CH·NHAr′ (VI.)

became of interest to study cases in which Ar and Ar′ are two different aryl nuclei. We have found that 3-nitro-6-methylquinoline is formed when (I; $R_1 = R_3 = H$, $R_2 = Me$) is refluxed with either aniline hydrochloride (40% yield) or *o*-toluidine hydrochloride (22% yield), but that if *m*-toluidine hydrochloride is used the product is 3-nitro-5-(or 7-)methylquinoline (35% yield), identical with that obtained from the same hydrochloride and (I; $R_1 = R_2 = H$, $R_3 = Me$). On the other hand, interaction of (I; $R_1 = R_2 = R_3 = H$) and *p*-toluidine hydrochloride gave 3-nitro-6-methylquinoline (16%), and no 3-nitroquinoline was isolated. The reaction between (I; $R_1 = R_2 = H$, $R_3 = Me$) and *p*-toluidine hydrochloride gave a product, m. p. 135—137°, which was not identical with any of the above compounds, and is possibly a mixture of nitromethylquinolines. No quinoline derivative was isolated from the product of reaction between *p*-toluidine hydrochloride and 2 : 4′-*dinitro*-2-*formylethylideneaniline* (I; $R_1 = R_3 = H$, $R_2 = NO_2$).

Further study of this reaction is necessary before its limitations and detailed mechanism can be stated with precision. However, the existing data can be given a simple qualitative interpretation if one assumes that the entity which is cyclised is the resonating kation (VII), which

(VII.) [Ar·NH:CH·C(NO_2):CH·NHAr′]$^+$ Ar·NH·CH:C(NO_2)·CH:NAr′ (VIII.)

could yield the 3-nitroquinoline by loss of arylamine and a proton. The behaviour of a series of such kations, in which Ar is the same and Ar′ is varied, would depend in any given case on

the distribution of the kationic charge, which would itself change with variations in the nature of Ar′; it is thus possible to account for the formation of two different products from 2-nitro-2-formylethylidene-*p*-toluidine when it is refluxed with the hydrochlorides of aniline, *p*-toluidine, or *o*-toluidine on the one hand, and with that of *m*-toluidine on the other. Further, the resonating ion (VII) is common to each of the bases (VI) and (VIII), and hence the formation of 3-nitro-6-methylquinoline from (*a*) 2-nitro-2-formylethylideneaniline and *p*-toluidine hydrochloride and (*b*) 2-nitro-2-formylethylidene-*p*-toluidine and aniline hydrochloride is readily explained. It is to be noted, however, that the two reaction-pairs—2-nitro-2-formylethylidene-*m*-toluidine–*p*-toluidine hydrochloride and 2-nitro-2-formylethylidene *p*-toluidine–*m*-toluidine hydrochloride—do not give identical products; further investigation is needed to show whether this result is a genuine discrepancy or has arisen from manipulative difficulties.

The monoanil (I; $R_1 = R_2 = R_3 = H$) and aniline readily yielded the dianil (V or VI; Ar = Ar′ = Ph) when boiled for a short time in acetic acid in the absence of mineral acid; in dilute aqueous hydrochloric acid this compound was rapidly hydrolysed to the monoanil and aniline.

The concept of cyclisation of a resonating kation of the type (VII) derivable from two formally tautomeric anils (VI) or (VIII) is merely a particular example of the more general case (IX), where R_1, R_2, and R_3 are substituents or hydrogen atoms, and could equally well be applied to other quinoline syntheses in which dianils or the type in question are believed to participate (*e.g.*, König, *Ber.*, 1923, **56**, 1853; Petrow, *loc. cit.*; Johnson, Woroch, and Mathews, *J. Amer. Chem. Soc.*, 1947, **69**, 566). In the Combes synthesis, however, in which a monoanil Ar·N:CR·CH_2·COR′ (or Ar·NH·CR:CH·COR′) is heated in concentrated sulphuric acid, the participation of (IX) is unlikely, because it could arise only by hydrolysis of the monoanil followed by disproportionation, and Roberts and Turner (*J.*, 1927, 1832) state, and we have confirmed, that the formation of 2 : 4 : 6-trimethylquinoline from (X) is quantitative. Furthermore, we find that, in contrast to this quantitative transformation, no quinoline derivative is formed when (X) is refluxed with *p*-toluidine hydrochloride in glacial acetic acid (the products

(IX.) $[Ar{\cdot}NH{:}CR_1{\cdot}CR_2{:}CR_3{\cdot}NHAr']^+$ p-Me·C_6H_4·NH·CMe:CH·COMe (X.)

(XI.) $Ar{\cdot}\overset{\overset{NAr''}{|}}{C}{\cdot}CHR{\cdot}NHAr'$

from short periods of refluxing were hydrolysable to *p*-toluidine, and longer refluxing gave a neutral compound, m. p. 151°, of obscure constitution and apparent formula $C_{17}H_{20}O_2N_2$).

The Bischler indole synthesis, according to recent evidence (*Ann. Reports*, 1946, **43**, 242; see also Cowper and Stevens, *J.*, 1947, 1041), also proceeds by way of an amine-anil intermediate (XI), which, however, differs from (IX) by virtue of the fact that addition of a proton to (XI) would give an ion which, unlike (IX), is not derivable from two different base tautomers. This formal difference between the two types of synthesis might have important practical consequences should the tautomeric forms of (XI), and those of the base derivable from (IX), prove to be not readily interconvertible.

Experimental.

(Melting points are uncorrected.)

Schiff Bases from Nitromalondialdehyde.—The following method, based on that of Hill and Torrey (*Amer. Chem. J.*, 1899, **22**, 95), gave consistent yields of 40% of sodionitromalondialdehyde. Mucobromic acid (20 g.) was added in one portion to a mechanically-stirred solution of sodium nitrite (20 g.) in water (50 c.c.) and alcohol (50 c.c.), and the temperature raised quickly to 50°; the spontaneous rise in temperature described by Hill and Torrey was not observed. After 10 minutes at 47—50°, the red solution was quickly cooled with vigorous stirring, and the yellow mass of sodionitromalondialdehyde collected (4·8 g.), washed with alcohol, and dried at 50°. The Schiff bases were all prepared by the same method, as illustrated by the following example. A freshly-prepared solution of sodionitromalondialdehyde (4·8 g.) in water (30 c.c.) was added in one portion to a solution of aniline hydrochloride (5 g.) in 2N-hydrochloric acid (15 c.c.). The 2-nitro-2-formylethylideneaniline which rapidly separated was collected after a few minutes (yield, 82%) and crystallised from alcohol; it then had m. p. 145—147° (Hill and Torrey give m. p. 143—144°). *2-Nitro-2-formylethylidene-o-toluidine* (80% yield), fine, pale yellow needles from alcohol, had m. p. 133—134° (Found : N, 14·1. $C_{10}H_{10}O_3N_2$ requires N, 13·6%). *2-Nitro-2-formylethylidene-m-toluidine* (81% yield) formed yellow prismatic needles, m. p. 156—157°, from alcohol or aqueous acetic acid (Found : N, 13·5%). 2-Nitro-2-formylethylidene-*p*-toluidine (yield, 80%) crystallised from alcohol or acetic acid in yellow needles, m. p. 179—180° (Hill and Torrey give m. p. 176—177°). *2 : 4′-Dinitro-2-formylethylideneaniline* (83% yield), soft yellow needles from acetic acid, had m. p. 230—231° (Found : N, 17·4. $C_9H_7O_5N_3$ requires N, 17·7%). *2 : 3′-Dinitro-2-formylethylidene-p-toluidine* (from the arylamine sulphate; yield 95%) formed soft yellow needles, m. p. 206—207° to a red liquid, from aqueous alcohol or aqueous acetic acid (Found : C, 47·8; H, 3·9; N, 16·6. $C_{10}H_9O_5N_3$ requires C, 47·8; H, 3·6; N, 16·7%); it was soluble in warm alkalis and was thereby hydrolysed to the arylamine, which separated when the solution was cooled.

3-Nitroquinoline.—A solution of aniline hydrochloride (0·67 g.) and 2-nitro-2-formylethylideneaniline

(1 g.) in acetic acid (10 c.c.) was refluxed for 17 hours. On cooling and dilution with water, a gum was precipitated from which the liquid (*A*) was decanted. 3-Nitroquinoline was isolated from (*A*) by basification (sodium hydroxide), and from the gum by extraction with warm 2N-hydrochloric acid followed by basification; total yield 0·37 g. (41%). The compound formed needles, m. p. 127—128°, and did not depress the m. p. of a sample prepared by the method of Uhle and Jacobs (*loc. cit.*). 2-Nitro-2-formylethylideneaniline was recovered unchanged after its solution in acetic acid had been refluxed for 24 hours, but in presence of 1 equiv. of aniline (in boiling acetic acid) the dianil was rapidly formed (brilliant yellow needles, m. p. 92—93°; Hill and Torrey give m. p. 93—94°). No quinoline derivative was isolated after equivalent amounts of the (mono)anil and aniline had been refluxed in acetic acid with 0·1 equiv. of aniline hydrochloride, but a mixture of 1 equiv. each of anil, aniline, and aniline hydrochloride gave *ca.* 10% of 3-nitroquinoline. The yield of the latter was not raised above 41% by the use of a mixture of anil and 2 equivs. of aniline hydrochloride.

3-*Nitro*-6-*methylquinoline.*—(*a*) A solution of 2-nitro-2-formylethylidene-*p*-toluidine (10 g.) and *p*-toluidine hydrochloride (7·6 g.) in acetic acid (50 c.c.) was gently refluxed for 16 hours. After dilution with an equal volume of water, 3-*nitro*-6-*methylquinoline* rapidly separated (7 g., 77%, m. p. 183—184° after being washed with a little cold acetic acid); it crystallised from absolute or aqueous ethanol in long, almost colourless prismatic needles, m. p. 185—186° (Found: C, 64·1; H, 4·3; N, 14·8. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3; N, 14·9%). The cyclisation was also tried in a less concentrated acetic acid solution, but the yield was smaller (0·73 g. from 2 g. of Schiff base). In both cases the reaction was incomplete after 7 hours' refluxing. 3-Nitro-6-methylquinoline and its analogues are sparingly soluble in water and fairly readily so in hot 2N-hydrochloric acid, but on cooling the free bases again separate; a mixture of a 3-nitroquinoline and an arylamine can be readily separated in this way.

(*b*) A mixture of 2-nitro-2-formyl-*p*-toluidine (0·44 g.) and powdered anhydrous zinc chloride (0·88 g.) was heated from 180° to 230° (bath temp.) during 3 minutes, and kept at 230° for 5 minutes. The cold mass was digested with hot water (50 c.c.), and the residue extracted with warm 5N-hydrochloric acid. Basification of the filtrate gave 3-nitro-6-methylquinoline (70 mg., 17·5%), m. p. 184—185° alone and mixed with authentic material.

3-*Amino*-6-*methylquinoline.*—Stannous chloride (3·9 g.) was added in portions during 20 minutes to a stirred solution of 3-nitro-6-methylquinoline (1 g.) in 10N-hydrochloric acid (6 c.c.); the temperature, which initially was not allowed to exceed 45°, was finally raised to 60° for 10 minutes with vigorous stirring. The suspension was then cooled, diluted, and made alkaline with sodium hydroxide, and the product was taken successively into ether and warm 0·5N-hydrochloric acid (charcoal). Basification of the acid solution at 0° gave 3-*amino*-6-*methylquinoline* [crude yield (m. p. 100—104°), 100%], which separated slowly from aqueous ethanol in fine white needles, m. p. 106—107° (Found: C, 75·7; H, 6·3; N, 17·9. $C_{10}H_{10}N_2$ requires C, 75·9; H, 6·4; N, 17·7%). The base, which showed a magnificent blue fluorescence in aqueous solution at pH 6, could be readily diazotised and coupled with alkaline β-naphthol.

3 : 5-*Dinitro*-6-*methylquinoline.*—3-Nitro-6-methylquinoline (8 g.) was added during 20 minutes with stirring to a mixture of nitric acid (*d* 1·53) and 65% oleum (60 c.c., 5 : 2 v/v) at −10° to −5°. After a further 10 minutes the temperature was allowed to rise to 0°, the solution poured on ice, and the solid (8·2 g., 83%, m. p. 163—164°) collected and crystallised from aqueous acetic acid and finally alcohol, from which 3 : 5-*dinitro*-6-*methylquinoline* separated in broad yellow blades, m. p. 167—168° (Found: C, 52·0; H, 3·2; N, 18·0. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0; N, 18·0%).

3-*Nitro*-5-(or 7-)*methylquinoline.*—A solution of 2-nitro-2-formylethylidene-*m*-toluidine (0·5 g.) and *m*-toluidine hydrochloride (0·38 g.) in acetic acid (2·5 c.c.) was refluxed for 17 hours. Dilution with water gave almost pure 3-*nitro*-5-(or 7-)*methylquinoline* (55%), which formed long, almost colourless, soft needles, m. p. 155—157°, from alcohol (Found: C, 63·85; H, 4·6; N, 14·9. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3; N, 14·9%).

3-*Nitro*-8-*methylquinoline.*—An exactly similar experiment to the above, but with *o*-toluidine derivatives and 15 hours' refluxing, gave a dark red solution, which was basified in the cold with 2N-sodium hydroxide. The resultant tar and suspension were extracted with ether, and the oil (0·48 g.) obtained by evaporation of the washed and dried extract was dissolved in aqueous ammoniacal alcohol; 3-*nitro*-8-*methylquinoline* (30 mg., 6·5%) separated, and formed bundles of slightly discoloured prismatic needles, m. p. 122—123° (Found: C, 64·0; H, 4·9; N, 15·3. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3; N, 14·9%).

Reactions of Schiff Bases with Salts of Various Arylamines.—The variations described in the theoretical section of this paper were all carried out using 0·4—0·5 g. of Schiff base and 1 equiv. of arylamine salt in 2·5—3 c.c. of acetic acid (15—17 hours' refluxing). The products were isolated as already described, and reaction mother-liquors were examined in cases where the total product was not extracted initially. The product from 2-nitro-2-formylethylidene-*m*-toluidine and *p*-toluidine hydrochloride formed colourless needles, m. p. 132—134°, not changed by crystallisation from aqueous alcohol or dilute hydrochloric acid; chromatography in benzene, using a 10 cm. column of alumina, was also virtually without effect, almost the whole of the material being recovered as a single fraction, m. p. 135—137° (softening at 133°) [135—144° when mixed with 3-nitro-5-(or 7-)methylquinoline].

Condensation of 2-p-*Toluidinopent*-2-*en*-4-*one and* p-*Toluidine Hydrochloride.*—The base, m. p. 69—70° (Roberts and Turner, *loc. cit.*, give m. p. 68—69°) (0·5 g.), and *p*-toluidine hydrochloride (0·4 g.) were refluxed for 24 hours in acetic acid (1 c.c.). The solid which slowly separated during 48 hours was crystallised from water, giving colourless needles, m. p. 150—151° (0·3 g.), of a *product* which was unchanged by crystallisation from aqueous alcohol or dilute ammonia and had no obvious basic properties (Found: C, 72·0; H, 7·47; N, 9·55, 9·9. $C_{17}H_{20}O_2N_2$ requires C, 71·8; H, 7·1; N, 9·85%). In alcoholic solution in presence of zinc chloride the condensation proceeded differently, but no single product could be isolated.

We are indebted to the Medical Research Council for a Research Studentship (J.S.M.).

WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY,
LIVERPOOL SCHOOL OF TROPICAL MEDICINE.

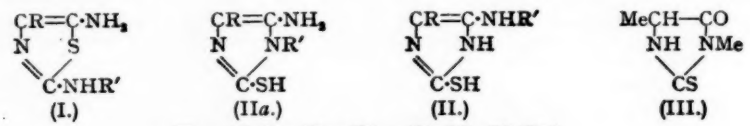
[*Received, January 30th,* 1948.]

411. *Studies in the Azole Series. Part IX. The Interaction of α-Amino-nitriles and Alkyl* iso*Thiocyanates.*

By A. H. Cook, J. D. Downer, and Sir Ian Heilbron.

Aminoacetonitrile and ethyl α-aminocyanoacetate react with methyl *iso*thiocyanate to give 5-amino-2-methylaminothiazoles (*e.g.*, IV). Unlike the corresponding 5-amino-2-acylaminothiazoles (Parts VI and VIII) which isomerise in the presence of mild alkali to give 5-acylamino-2-mercaptoglyoxalines, the 5-amino-2-methylaminothiazoles give 5-amino-2-mercapto-1-methylglyoxalines (*e.g.*, VII).

Previous papers in this Series (Parts VI and VIII, this vol., pp. 1262, 1340) showed that acyl-*iso*thiocyanates react with α-amino-nitriles to give substituted 2 : 5-diaminothiazoles (I) which rearrange in presence of mild alkali to give 5-acylamino-2-mercaptoglyoxalines (II) presumably through the intermediate (II*a*). In the case of ethyl α-aminocyanoacetate, however, the



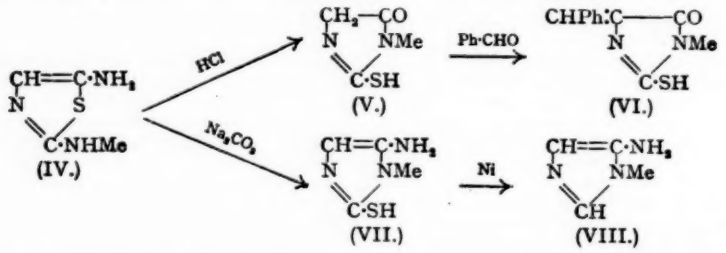
(I.) (II*a*.) (II.) (III.)

(R = H, Me, Ph; R′ = Ph·CO, CO_2Et.)

products obtained by reaction with either benzoyl or carbethoxy-*iso*thiocyanate, containing two strongly electronegative groups (I; R = CO_2Et, R′ = CO_2Et or PhCO), failed to give any cyclic isomeride on treatment with alkali. It was then thought that this stability might be overcome by introducing a more electropositive substituent in place of the acyl group in the 2-position of the thiazole. Accordingly, the present paper describes the reaction between α-amino-nitriles and methyl *iso*thiocyanate and the rearrangement of the products in alkali.

Mouneyrat and later Delépine (*Bull. Soc. chim.*, 1903, **29**, 1198) examined this reaction in the case of α-aminopropionitrile, obtaining a crude viscous reaction product which they failed to purify but which gave 3 : 5-dimethyl-2-thiohydantoin (III) on acid hydrolysis.

It has now been established that equivalent quantities of aminoacetonitrile and methyl *iso*thiocyanate afford a base which can be diazotised. Having regard to reactions discussed in earlier parts of this series it is formulated as *5-amino-2-methylaminothiazole* (IV). Its hydrolysis with concentrated hydrochloric acid gave 3-methyl-2-thiohydantoin (V) which was further identified by the preparation of its *5-benzylidene* derivative (VI). The formation of (V) is



paralleled by the hydrolysis of 5-amino-2-benzamidothiazole (Part VI of this series). On adding (IV) to dilute aqueous sodium carbonate an exothermic reaction took place with the formation of a pseudo-acidic isomeride which also exhibited basic properties; thus it formed a *hydrochloride*, combined with methyl *iso*cyanate, and underwent diazotisation. These reactions seemed incompatible with the glyoxaline structure (II; R = H, R′ = Me) already proved in earlier cases. It was soon evident, however, that the rearrangement had stopped at the intermediate stage (II*a*; R = H, R′ = Me), because refluxing the isomeride with concentrated hydrochloric acid resulted in the isolation of 3-methyl-2-thiohydantoin. The product of rearrangement was therefore formulated as *5-amino-2-mercapto-1-methylglyoxaline* (VII), desulphurisation affording *5-amino-1-methylglyoxaline* (VIII) which was unstable but formed a stable *monopicrate* and could be diazotised.

These results encouraged further study employing ethyl α-aminocyanoacetate in place of aminoacetonitrile. This amino-nitrile with methyl *iso*thiocyanate gave *5-amino-2-methylamino-4-carbethoxythiazole* (I; R = CO_2Et, R′ = Me), which was characterised by its ability to

diazotise and by the formation of a stable *hydrochloride, benzylidene* derivative, and a diacetyl derivative, *5-acetamido-2-methylimino-4-carbethoxy-3-acetylthiazoline*. The formation of a Schiff's base showed the more basic nature of the parent thiazole compared with the corresponding 5-acylaminothiazoles which failed to react in this way. Refluxing (I; R = CO_2Et, R′ = Me) with aqueous sodium carbonate gave the isomeride, *5-amino-2-mercapto-4-carbethoxy-1-methylglyoxaline* (II*a*; R = CO_2Et, R′ = Me), exhibiting both basic and pseudo-acidic properties. Its constitution was confirmed by vigorous hydrolysis which, removing the 4- and 5-substituents, gave 3-methyl-2-thiohydantoin. Further, it diazotised, and the diazonium salt coupled with β-naphthol to give a red dye. The glyoxaline was readily desulphurised by Raney nickel to give *5-amino-4-carbethoxy-1-methylglyoxaline* (cf. VIII), which gave a *hydrochloride* and could be diazotised. Both the glyoxaline (II*a*; R = CO_2Et, R′ = Me) and its desulphurisation product failed to react with sodium cyanate under the usual conditions.

Heating the thiazole (I; R = CO_2Et, R′ = Me) with ethanolic ammonia gave *5-amino-2-mercapto-4-carbamido-1-methylglyoxaline* by amide formation and rearrangement of the kind discussed above; it also exhibited basic and pseudo-acidic properties. It was desulphurised by Raney nickel to give *5-amino-4-carbamido-1-methylglyoxaline* which also diazotised. All attempts to cyclise the latter compound to a purine, using ethyl carbonate (cf. Sarasin and Wegmann, *Helv. Chim. Acta*, 1924, **7**, 713) or ethyl chloroformate (Mann and Porter, *J.*, 1945, 751) were unsuccessful, the glyoxaline being recovered. With carbonyl chloride only the *hydrochloride* of the parent base was obtained.

Phenyl *iso*thiocyanate was also allowed to react with ethyl α-aminocyanoacetate, but the product, presumably (I; R = CO_2Et, R′ = Ph) since it readily united with a further molecule of phenyl *iso*thiocyanate, proved much more stable towards alkali than products obtained when using methyl *iso*thiocyanate.

Experimental.

5-Amino-2-methylaminothiazole.—A solution of methyl *iso*thiocyanate (24·5 c.c.) in ether (25 c.c.) was added slowly to aminoacetonitrile (20 g.) in ether (150 c.c.) at 0° with stirring in nitrogen. The crude oil slowly solidified on continued stirring to give a brownish solid (30 g.), m. p. 97°, which when stirred in ethanol, filtered off, and washed with ether gave colourless prisms (21 g.), m. p. 98°. Crystallisation from ethyl acetate (4 vols.) or ethanol (3 vols.) gave almost colourless prisms of *5-amino-2-methylaminothiazole*, m. p. 100° (Found: C, 37·4; H, 5·6; N, 32·7. $C_4H_7N_3S$ requires C, 37·2; H, 5·5; N, 32·5%). Light absorption (chloroform): $\lambda_{inflex.}$ = 2420 A., ϵ = 12,900.

The preceding thiazole (1 g.) was boiled with concentrated hydrochloric acid (8 c.c.) for 5 mins., water (15 c.c.) added, the solution cooled, and the colourless prismatic needles of 3-methyl-2-thiohydantoin (0·5 g.) filtered off and washed with a little ethanol; m. p. and mixed m. p. with authentic material, 162° (Marckwald, Neumark, and Stelzner, *Ber.*, 1891, **24**, 3285, quote m. p. 162°) (Found: C, 37·3; H, 4·75; S, 24·9. Calc. for $C_4H_6ON_2S$: C, 36·9; H, 4·65; S, 24·6%).

3-Methyl-2-thiohydantoin (0·5 g.), dissolved in acetic acid (4·5 c.c.) containing fused sodium acetate (0·6 g.) and benzaldehyde (0·6 c.c.), was heated in an oil-bath at 140° for 1 hour. On cooling, the yellow needles (0·6 g.), m. p. 205°, were filtered off and washed with ethanol and ether. Crystallisation from ethanol (100 vols.) gave long yellow needles of *5-benzylidene-3-methyl-2-thiohydantoin*, m. p. 204° (Found: C, 60·5; H, 4·4; N, 12·5; S, 14·9. $C_{11}H_{10}ON_2S$ requires C, 60·5; H, 4·6; N, 12·8; S, 14·7%). The 3-methyl-2-thiohydantoin obtained from 5-amino-2-methylaminothiazole above, gave the same benzylidene derivative, m. p. and mixed m. p. 204°.

5-Amino-2-mercapto-1-methylglyoxaline.—5-Amino-2-methylaminothiazole (10 g.) was mixed with 10% aqueous sodium carbonate (25 c.c.); an exothermic reaction immediately commenced and was completed by heating on the steam-bath under nitrogen for 5 minutes, a clear solution being obtained. The thick crystalline precipitate which formed on cooling was stirred with water (20 c.c.) containing a trace of sodium hydrogen sulphite, filtered off, and washed with a little water, ethanol, and finally ether to give colourless prismatic rods (6·5 g.), m. p. 148°, which rapidly darkened on exposure to air. Crystallisation from methanol (10 vols.) gave almost colourless needles, of *5-amino-2-mercapto-1-methylglyoxaline*, m. p. 151° (decomp.) (Found: C, 37·5; H, 5·6; N, 32·3; S, 24·4. $C_4H_7N_3S$ requires C, 37·2; H, 5·5; N, 32·5; S, 24·8%). Light absorption (ethanol): $\lambda_{max.}$ = 2670 A., ϵ = 13,550.

Boiling the above glyoxaline (0·9 g.) for 2 minutes with concentrated hydrochloric acid (5 c.c.) and crystallisation of the product from ethanol–ether gave colourless silky needles of *5-amino-2-mercapto-1-methylglyoxaline hydrochloride* (0·4 g.), m. p. 222° (decomp.) (Found: N, 25·0; S, 18·9. $C_4H_8N_3ClS$ requires N, 25·4; S, 19·4%). It could be diazotised, and the diazonium salt coupled with β-naphthol to give a red dye.

Refluxing 5-amino-2-mercapto-1-methylglyoxaline (0·5 g.) in concentrated hydrochloric acid (5 c.c.) for 2 hours, cooling, and filtering gave colourless irregular prisms of 3-methyl-2-thiohydantoin (0·2 g.), m. p. and mixed m. p. with an authentic specimen 162°.

5-Amino-2-mercapto-1-methylglyoxaline (1·5 g.), pyridine (8 c.c.), and methyl *iso*cyanate (1·2 c.c.) were refluxed gently for 10 minutes, a crystalline solid (1·0 g.), m. p. 211°, separating. Crystallisation from ethyl acetate–methanol gave colourless micro-crystals of *5-methylureido-2-mercapto-1-methylglyoxaline*, m. p. 212° (Found: C, 39·1; H, 5·5; N, 29·8; S, 17·1. $C_6H_{10}ON_4S$ requires C, 38·7; H, 5·4; N, 30·1; S, 17·2%).

5-Amino-2-mercapto-1-methylglyoxaline (3 g.) was refluxed in ethanol (20 c.c.) with Raney nickel (*ca.* 4 g.) for 40 minutes. Evaporation of the filtrate in a vacuum gave colourless irregular prisms of

5-amino-1-methylglyoxaline (1·3 g.), m. p. 101° (decomp.), which rapidly decomposed in air. It formed a stable *monopicrate*, m. p. 177° (Found : C, 36·8; H, 3·3; N, 26·4. $C_{10}H_{10}O_7N_6$ requires C, 36·8; H, 3·1; N, 25·8%). The base formed a deliquescent hydrochloride with ethanolic hydrochloric acid which could be diazotised, the diazonium salt coupling with β-naphthol to give a red dye.

5-Amino-2-methylamino-4-carbethoxythiazole.—A solution of methyl *iso*thiocyanate (14 c.c.) in ether (15 c.c.) was added to a solution of ethyl α-aminocyanoacetate (26 g.) in ether (100 c.c.), and the clear solution kept overnight. The colourless crystals (30·5 g.), m. p. 162°, which had deposited were filtered off and washed with ether. The filtrate, after several days, gave a further crop of crystals (5 g.), m. p. 162°. Crystallisation from ethanol (10 vols.) gave colourless irregular prismatic rods of *5-amino-2-methylamino-4-carbethoxythiazole*, m. p. 162° (decomp.) (Found : C, 42·0; H, 5·6; N, 20·8; S, 16·0. $C_7H_{11}O_2N_3S$ requires C, 41·8; H, 5·5; N, 20·9; S, 15·9%). Light absorption (chloroform) : $\lambda_{max.}$ = 2600, 3080, 3050 A.; ϵ = 10,850, 9,050, 9,050, respectively. It was soluble in dilute hydrochloric acid and could be diazotised.

The preceding thiazole (1 g.) on boiling with 3% ethanolic hydrochloric acid (30 c.c.) gave colourless micro-needles of *5-amino-2-methylamino-4-carbethoxythiazole hydrochloride*, m. p. 140° (decomp.) (Found : S, 13·3. $C_7H_{12}O_2N_3SCl$ requires S, 13·5%).

Refluxing 5-amino-2-methylamino-4-carbethoxythiazole (2 g.) with benzaldehyde (1 c.c.) in ethanol (20 c.c.) for 20 minutes and cooling gave a bright yellow solid (0·8 g.), m. p. 180°, which on recrystallisation from ethanol (25 c.c.) gave yellow prismatic needles of the *benzylidene* derivative (0·5 g.), m. p. 182° (Found : C, 57·7; H, 5·1; N, 14·6; S, 11·0. $C_{14}H_{15}O_2N_3S$ requires C, 58·0; H, 5·2; N, 14·5; S, 11·1%). Light absorption (chloroform) : $\lambda_{max.}$ = 2480, 3910 A.; ϵ = 14,450, 18,775, respectively.

5-Amino-2-methylamino-4-carbethoxythiazole (1·5 g.) was refluxed in acetic anhydride (10 c.c.) for 15 minutes, the cold solution stirred with iced water (70 c.c.) for 15 minutes, and the crude product (2 g.), m. p. 197°, filtered off and washed with water. Crystallisation from ethanol (90 c.c.) gave colourless needles of *5-acetamido-2-methylimino-4-carbethoxy-3-acetylthiazoline* (1·7 g.), m. p. 197° (Found : C, 46·1; H, 5·2; N, 14·6; S, 11·3. $C_{11}H_{15}O_4N_3S$ requires C, 46·3; H, 5·3; N, 4·7; S, 11·2%). Light absorption (chloroform) : $\lambda_{max.}$ = 2780, 3070 A.; ϵ = 13,400, 10,850, respectively.

5-Amino-2-mercapto-4-carbethoxy-1-methylglyoxaline.—5-Amino-2-methylamino-4-carbethoxythiazole (12 g.) was refluxed for 45 minutes in 10% aqueous sodium carbonate (150 c.c.), and the crystalline solid (2·3 g.), m. p. 210°, deposited on cooling was filtered off (see below). Crystallisation from ethanol (40 c.c.) (charcoal) gave colourless prisms of *5-amino-2-mercapto-4-carbethoxy-1-methylglyoxaline*, m. p. 211° (decomp.) (Found : C, 42·4; H, 5·5; N, 21·2; S, 15·7. $C_7H_{11}O_2N_3S$ requires C, 41·8; H, 5·5; N, 20·9; S, 15·9%). Light absorption (ethanol) : $\lambda_{max.}$ = 2280, 2690, 3070 A.; ϵ = 9,050, 10,050, 22,100, respectively. It dissolved in hot aqueous sodium carbonate with a red coloration, was sparingly soluble in dilute hydrochloric acid, and could be diazotised. The filtrate (see above) was neutralised and evaporated to dryness in a vacuum. The residue was extracted with hot methanol (200 c.c.), and the extract concentrated to 40 c.c. and diluted with ether (150 c.c.). Repeated crystallisation from ethyl acetate–ethanol of the cream solid (8 g.), m. p. 271° (decomp.), which was precipitated, gave colourless micro-plates of a *compound*, m. p. 273° (decomp.) (Found : C, 32·0; H, 4·2; N, 30·3; S, 17·5. $C_5H_6O_2N_4S$ requires C, 31·9; H, 4·3; N, 29·8; S, 17·0%). Light absorption (ethanol) : $\lambda_{max.}$ = 2560, 2930 A.; ϵ = 11,275, 13,450, respectively. It dissolved in dilute aqueous sodium carbonate, giving a red coloration. On refluxing the preceding compound (1·5 g.) for 20 minutes with 30% hydrochloric acid (12 c.c.), vigorous effervescence occurred, and on cooling cream prisms (0·9 g.) of 3-methyl-2-thiohydantoin, m. p. and mixed m. p. with authentic material 162°, crystallised.

5-Amino-2-mercapto-4-carbethoxy-1-methylglyoxaline (1 g.) was refluxed in ethanol (20 c.c.) with Raney nickel (*ca.* 3 g.) for 45 minutes. The filtrate was evaporated to dryness in a vacuum, and the crude product (0·7 g.) crystallised from ethyl acetate–ethanol, giving colourless rods of *5-amino-4-carbethoxy-1-methylglyoxaline*, m. p. 192° (Found : C, 50·0; H, 6·2; N, 24·8. $C_7H_{11}O_2N_3$ requires C, 49·7; H, 6·5; N, 24·8%). Light absorption (ethanol) : $\lambda_{max.}$ = 2685 A.; ϵ = 13,775. It dissolved in dilute hydrochloric acid and could be diazotised. Dissolving the base (1·5 g.) in hot ethanol (15 c.c.) containing 6% ethanolic hydrogen chloride (12 c.c.) and diluting with ether (55 c.c.) gave colourless needles (1·5 g.) of *5-amino-4-carbethoxy-1-methylglyoxaline hydrochloride*, m. p. 203° (decomp.) (Found : C, 40·6; H, 5·8; N, 20·4. $C_7H_{12}O_2N_3ClS$ requires C, 40·9; H, 5·9; N, 20·4%).

5-Amino-2-methylamino-4-carbethoxythiazole (4 g.) was heated at 100—110° with ethanol (25 c.c.) and liquid ammonia (5 c.c.) for 24 hours (sealed tube). The crystals (2·2 g.), m. p. 245° (decomp.), crystallised from a large volume of methanol to give colourless irregular prisms of *5-amino-2-mercapto-4-carbamido-1-methylglyoxaline*, m. p. 251° (decomp.) (Found : C, 35·0; H, 5·0; N, 33·0; S, 17·9. $C_5H_8ON_4S$ requires C, 34·9; H, 4·7; N, 32·6; S, 18·6%). Light absorption (ethanol) : $\lambda_{max.}$ = 2680, 3030 A.; ϵ = 9,975, 18,925, respectively. It dissolved in dilute hydrochloric acid and could be diazotised. It gave a red solution in alkali.

The preceding glyoxaline (2·7 g.) was refluxed for 40 minutes in ethanol (220 c.c.) with Raney nickel (*ca.* 6 g.). The crude product (1·9 g.) obtained by evaporation in a vacuum of the filtrate crystallised from ethanol (100 vols.) to give colourless scintillating needles of *5-amino-4-carbamido-1-methylglyoxaline*, m. p. 254° (decomp.) (Found : C, 42·9; H, 6·0; N, 38·6. $C_5H_8ON_4$ requires C, 42·8; H, 5·8; N, 40·0%). Light absorption (ethanol) : $\lambda_{max.}$ = 2680 A.; ϵ = 13,300. Heating it with a 20% toluene solution of carbonyl chloride (0·5 g. in 12 c.c.) at 170° (sealed tube) for 16 hours gave 5-amino-4-carbamido-1-methylglyoxaline hydrochloride (0·55 g.), m. p. 257°, which reverted to the base on neutralisation.

Phenyl *iso*thiocyanate (24 c.c.) was added to ethyl α-aminocyanoacetate (26 g.) in ether (100 c.c.) and the mixture allowed to reflux gently. After standing overnight the colourless needles (46 g.), m. p. 200°, were filtered off and crystallised from ethanol to give colourless prisms of *5-amino-2-anilino-4-carbethoxythiazole*, m. p. 200° (Found : C, 54·6; H, 5·1; N, 15·8. $C_{12}H_{13}O_2N_3S$ requires C, 54·7; H, 5·0; N, 16·0%). Light absorption (chloroform) : $\lambda_{max.}$ = 2910 A.; ϵ = 14,750.

The preceding thiazole (2 g.) was dissolved in pyridine (9 c.c.) and boiled for 1 minute with phenyl *iso*thiocyanate (1 c.c.). On cooling and dilution with methanol (40 c.c.) a yellow solid (1·6 g.), m. p. 218°, was obtained which crystallised from dioxan to give yellow needles of *5-phenylthioureido-2-anilino-*

4-carbethoxythiazole, m. p. 218° (Found : N, 14·0. $C_{19}H_{18}O_2N_4S_2$ requires N, 14·1%). Light absorption (dioxan) : $\lambda_{max.}$ = 2900, 3700 A.; ϵ = 26,650, 13,350, respectively.

The authors thank Dr. E. A. Braude for the determination of absorption spectra.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

[*Received, February 6th* 1948.]

---

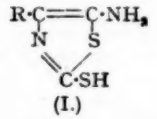
412. *Studies in the Azole Series. Part X. Some 5-Amino-2-mercapto-4-alkylthiazoles and 2 : 4-Dithio-5-alkylhydantoins.*

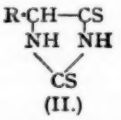
By A. H. COOK, SIR IAN HEILBRON, and E. S. STERN.

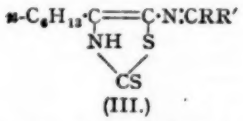
Reaction of various aliphatic α-amino-nitriles with carbon disulphide gives 5-amino-2-mercapto-4-alkylthiazoles which are readily isomerised to dithiohydantoins on warming with alkali.

IN previous papers in this series (Cook, Heilbron, and Levy, Part II, *J.*, 1947, 1598; Part III, this vol., p. 201) it was observed that the stability of 5-amino-2-mercaptothiazoles (I) varies greatly with the substituent in the 4-position. Thus (I; R = Ph) was readily obtainable from α-aminobenzyl cyanide and was quite stable when pure, though it rearranged to the isomeric dithiohydantoin (II; R = Ph) on boiling with alkali. Aminopropionitrile, on the other hand, in reaction with carbon disulphide gave the dithiohydantoin (II; R = Me) immediately, the intermediate thiazole only being isolated when the reaction was carried out in the presence of a carbonyl compound, *e.g.*, in acetone, whereupon the Schiff's base was produced. The present paper describes thiazoles of the type (I) in which R is a higher alkyl group; the substituents chosen were the *n*-hexyl, the 1-ethylamyl, and the ω-carbethoxy-*n*-butyl groups.

It was found that on reaction of the appropriate α-amino-nitrile with carbon disulphide comparatively low-melting *aminomercaptothiazoles* [I; R = *n*-C_6H_{13}, Bu^n·CHEt, or CO_2Et·Bu^n, respectively] were produced; these were quite stable when pure but on warming with alkali or even on prolonged standing in solution they isomerised to the corresponding *dithiohydantoins* (II). The thiazole (I; R = *n*-C_6H_{13}) condensed readily with carbonyl compounds giving *Schiff's bases* (III; R = H, R′ = *n*-C_6H_{13}, or R = R′ = Me); the thiazoles (I) condensed with glyoxal (Part II, *loc. cit.*) and the purple colour obtained served to distinguish them from the isomeric dithiohydantoins (II). Acetylation of (I; R = *n*-C_6H_{13} and R = Bu^n·CHEt) proceeded with great ease in acetic anhydride, and as the *acetyl* derivatives failed to react with carbonyl compounds they must be the 5-acetamido-compounds. Methylation, on the other hand, by contrast with the phenyl analogue (I; R = Ph), usually failed to give a solid methylthio-derivative though *5-acetamido-2-methylthio-4-n-hexylthiazole* was suitable for the characterisation of the parent thiol compound.


(I.)


(II.)


(III.)

The structure of the dithiohydantoins (II; R = *n*-C_6H_{13} and R = Bu^n·CHEt) was established by desulphurisation with aqueous chloroacetic acid (Johnson *et al.*, *J. Amer. Chem. Soc.*, 1912, **34**, 1041) to the corresponding hydantoins, which were independently prepared by the method of Henze and Speer (*J. Amer. Chem. Soc.*, 1942, **64**, 522).

The above thiazoles were selected because the products appeared to bear some structural relationship to biotin; accordingly, several of the resulting thiazoles and dithiohydantoins were tested for biotin activity at the laboratories of the Distillers Co. Ltd., Great Burgh, Epsom, by Mr. J. S. Harrison, to whom the authors are much indebted. These tests showed no growth-promoting effect for either *L. casei* or *Sacch. cerevisiæ*; a slight growth-inhibitory effect could not be reversed by addition of biotin and appears to be due to the general toxicity of these compounds.

EXPERIMENTAL.

Heptaldehyde had b. p. 53°/19 mm., $n_D^{20°}$ 1·4113, and the cyanohydrin had b. p. 140°/19 mm., n_D^{19} 1·4351.

1-Amino-*n*-octyl cyanide (cf. Erlenmeyer and Sigel, *Annalen*, 1875, **177**, 125) was obtained by treating the above cyanohydrin (15 g.) in ethanol (15 c.c.) with liquid ammonia (30 c.c.) overnight at room

temperature. The *hydrochloride* (15 g.), precipitated from ether, crystallised from ethyl acetate in needles, m. p. 141—142° (Found: C, 54·4; H, 9·6; N, 15·5. $C_6H_{17}N_2Cl$ requires C, 54·4; H, 9·7; N, 15·85%). Regeneration of the base yielded an oil which on distillation gave an unidentified *oil*, b. p. 100°/10^{-3} mm., $n_D^{18°}$ 1·4500 (Found: C, 74·8; H, 11·5; N, 11·8%); on treatment with ethereal hydrochloric acid this gave the hydrochloride described above.

5-*Amino*-2-*mercapto*-4-n-*hexylthiazole* (as I).—The above hydrochloride (48 g.) was neutralised with sodium hydrogen carbonate, and the base extracted into light petroleum (b. p. 40—60°); addition of carbon disulphide (24 g.) in light petroleum afforded, after standing for 6 hours at 0° under nitrogen, 5-*amino*-2-*mercapto*-4-n-*hexylthiazole* (21 g.) which crystallised from ethyl acetate–light petroleum in pale yellow needles, m. p. 113° (Found: C, 50·4; H, 7·4; N, 12·7; S, 29·6. $C_9H_{16}N_2S_2$ requires C, 50·0; H, 7·5; N, 13·0; S, 29·6%). Light absorption: $\lambda_{max.}$ in ethanol = 3340 A., ϵ = 11200; in 20% aqueous ammonia $\lambda_{max.}$ = 3040 A., ϵ = 5500. Acetylation of the thiazole (2 g.) with acetic anhydride (10 c.c.) gave 5-*acetamido*-2-*mercapto*-4-*hexylthiazole* (2 g.), which crystallised from ether–benzene in needles, m. p. 175° (Found: C, 51·6; H, 7·0; N, 10·65. $C_{11}H_{18}ON_2S_2$ requires C, 51·1; H, 7·0; N, 10·85%). Light absorption: maximum in ethanol at 3370 A., ϵ = 16,000.

Treatment of the acetyl compound (1 g.) in 2N-sodium hydroxide (10 c.c.) with methyl sulphate (0·5 g.) at 0° yielded 5-*acetamido*-2-*methylthio*-4-n-*hexylthiazole* (1·2 g.), which formed needles from ethyl acetate–light petroleum, m. p. 85·5° (Found: C, 53·2; H, 7·4; N, 10·4; S, 24·1. $C_{12}H_{20}ON_2S_2$ requires C, 52·9; H, 7·4; N, 10·3; S, 23·5%). Light absorption in ethanol: $\lambda_{max.}$ = 2500, 2560, and 2990 A., ϵ = 3600, 3600, and 12,000 respectively.

5-n-*Heptylideneamino*-2-*mercapto*-4-n-*hexylthiazole* (III; R = H, R′ = *n*-C_6H_{13}) was obtained from the thiazole (I; R = *n*-C_6H_{13}) by addition of heptaldehyde. It crystallised from ethyl acetate–light petroleum in very pale yellow needles, m. p. 113° (Found: C, 61·7; H, 8·95; N, 8·7; S, 21·0. $C_{16}H_{28}N_2S_2$ requires C, 61·4; H, 9·0; N, 8·5; S, 20·5%). Light absorption maxima in ethanol: 2280, 2400, and 3370 A.; ϵ = 6500, 6300, and 12,500, respectively. This substance (8·5 g.) was also obtained by treating (A), from the distilled α-amino-*n*-octyl cyanide (10 g.), with carbon disulphide (5 g.) in light petroleum.

Treatment of the thiazole (I; R = *n*-C_6H_{13}) with acetone, or addition of carbon disulphide to α-amino-*n*-octyl cyanide in acetone, afforded 2-*mercapto*-5-iso*propylideneamino*-4-n-*hexylthiazole* (III; R = R′ = Me), m. p. 99—100° (Found: N, 10·6; S, 25·5. $C_{12}H_{20}N_2S_2$ requires N, 10·9; S, 25·0%).

The thiazole (I; R = *n*-C_6H_{13}) (2 g.) with pyridine (10 c.c.) on refluxing for 10 minutes gave a *bis-compound* (1·8 g.) (cf. the behaviour of I, R = Ph; Part II of this series), soluble in aqueous sodium hydroxide and in excess of pyridine but insoluble in ammonia. It crystallised from dioxan–water in yellow needles, m. p. 212—215° (decomp.) (Found: C, 50·6; H, 6·9; N, 12·9; S, 29·6. $C_{18}H_{30}N_4S_4$ requires C, 50·2; H, 7·0; N, 13·0; S, 29·8%). Light absorption in ethanol: $\lambda_{max.}$ = 2230, 2650, 3370 A.; ϵ = 13,500, 21,500, and 5600, respectively.

2 : 4-*Dithio*-5-n-*hexylhydantoin* (II; R = *n*-C_6H_{13}).—Treatment of the thiazole (I; R = C_6H_{13}) (5 g.) with hot 2N-sodium hydroxide for 10 minutes or with hot saturated aqueous potassium carbonate (20 c.c.) for 1 hour under nitrogen afforded on acidification 2 : 4-*dithio*-5-n-*hexylhydantoin* (4·8 g.), a colourless solid which very rapidly became yellow, and on crystallisation from ethyl acetate had m. p. 233—234° (decomp.) (Found: C, 49·3; H, 7·0; S, 29·5. $C_9H_{16}N_2S_2$ requires C, 50·0; H, 7·5; S, 29·6%). Light absorption maxima in ethanol: 2420 and 3220 A.; ϵ = 6500 and 15,000, respectively; in 20% aqueous ammonia: maximum at 3340 A., ϵ = 8500. This dithiohydantoin was also obtained by treating 1-amino-*n*-octyl cyanide (5 g.) and carbon disulphide (2·5 g.) with a suspension of potassium carbonate (4·2 g.) in ethanol (35 c.c.) for 3 hours at 60° under nitrogen. It was soluble in ammonia and carbonate solution but insoluble in bicarbonate or 1N-sodium acetate. Acetylation of (II; R = *n*-C_6H_{13}) (0·5 g.) with acetic anhydride (5 c.c.) and sulphuric acid (0·1 c.c.) gave the *monoacetyl* compound (0·4 g.), separating from ethyl acetate–light petroleum in needles, m. p. 155° (Found: C, 50·3; H, 7·0; S, 25·3. $C_{11}H_{18}ON_2S_2$ requires C, 51·1; H, 7·0; S, 24·8%). Dithio-*n*-hexylhydantoin (0·8 g.) with chloroacetic acid (0·8 g.) in water (5 c.c.) on refluxing for 30 minutes under nitrogen gave 4-*n*-hexylhydantoin (0·6 g.), m. p. 146°, undepressed by authentic material prepared by Henze and Speer's method (*loc. cit.*).

2-Ethyl-*n*-hexanal had b. p. 160°, $n_D^{22°}$ 1·4152 (cf. Weizmann *et al.*, *Chem. and Ind.*, 1937, **56**, 587). The *cyanohydrin* had b. p. 86·5°/0·05 mm., $n_D^{19°}$ 1·4419 (Found: C, 69·8; H, 11·1; N, 9·0. $C_9H_{17}ON$ requires C, 69·5; H, 11·0; N, 9·0%). Treatment of the cyanohydrin (15 g.) with liquid ammonia (25 c.c.) in ethanol (15 c.c.) and standing overnight afforded 1-amino-2-ethyl-*n*-hexyl cyanide, the *hydrochloride* (8·5 g.) of which crystallised from ethyl acetate in needles, m. p. 139° (Found: C, 56·6; H, 10·0; N, 15·0. $C_9H_{18}N_2Cl$ requires C, 56·65; H, 10·0; N, 14·7%).

5-*Amino*-2-*mercapto*-4-1′-*ethyl*-n-*amylthiazole*.—Regeneration of the preceding base from the hydrochloride (3 g.), extraction with light petroleum, and reaction with carbon disulphide (2 g.) afforded 5-*amino*-2-*mercapto*-4-1′-*ethyl*-n-*amylthiazole* (1 g.) which crystallised from ethyl acetate–light petroleum in pale yellow needles, m. p. 79° (decomp.) (Found: C, 52·5; H, 8·0; N, 11·7. $C_{10}H_{18}N_2S_2$ requires C, 52·1; H, 7·9; N, 12·2%). Light absorption maximum in ethanol at 3390 A., ϵ = 11,500, and in 20% ammonia at 3040 A., ϵ = 7500. Acetylation with acetic anhydride gave the 5-*acetamido*-derivative, crystallising from ethyl acetate–light petroleum in very pale yellow needles, m. p. 200—201° (decomp.) (Found: C, 52·5; H, 7·3; N, 9·7. $C_{12}H_{20}ON_2S_2$ requires C, 52·9; H, 7·4; N, 10·3%). Light absorption maximum in ethanol at 3310 A., ϵ = 14,500.

2 : 4-*Dithio*-5-1′-*ethyl*-n-*amylhydantoin* was obtained by alkali treatment of the thiazole; the colourless compound on crystallisation from ethyl acetate gave pale yellow needles, m. p. 258° (decomp.) (Found: C, 52·3; H, 8·1; S, 26·8. $C_{10}H_{16}N_2S_2$ requires C, 52·1; H, 7·9; S, 27·8%). The dithiohydantoin (0·15 g.) on refluxing with 20% aqueous chloroacetic acid (2 c.c.) gave 5-1′-*ethyl*-n-*amylhydantoin* (0·1 g.), m. p. 145—146° (Found: C, 60·3; H, 8·9; N, 13·7. $C_{10}H_{18}O_2N_2$ requires C, 60·6; H, 9·15; N, 14·1%), identical with a sample prepared by the method of Henze and Speer (*loc. cit.*).

ω-Carbethoxy-*n*-valeraldehyde, prepared by the method of Baker *et al.* (*J. Org. Chem.*, 1947, **12**, 163), had b. p. 93°/1 mm., $n_D^{25°}$ 1·4305; the *cyanohydrin* had b. p. 138°/0·01 mm., $n_D^{21°}$ 1·4471 (Found: C, 58·5; H, 8·3. $C_9H_{15}O_2N$ requires C, 58·35; H, 8·15%). Treatment of the cyanohydrin (12 g.) in

ethanol (20 c.c.) with liquid ammonia (20 c.c.) gave α-amino-ω-carbethoxyhexonitrile, which was isolated as its oxalate.

5-Amino-2-mercapto-4-ω-carbethoxy-n-butylthiazole was obtained by regeneration of the base from the above oxalate and reaction with carbon disulphide. It crystallised from ethyl acetate–light petroleum in very pale yellow needles, m. p. 65° (decomp.) (Found: C, 46·1; H, 6·2; N, 10·8. $C_{10}H_{16}O_2N_2S_2$ requires C, 46·1; H, 6·2; N, 10·8%).

2 : 4-Dithio-5-ω-carbethoxy-n-butylhydantoin, obtained by treatment of the thiazole with a suspension of potassium carbonate in ethanol at 60° for 3 hours under nitrogen, crystallised from ethyl acetate–light petroleum and had m. p. 199—200° (Found: C, 46·65; H, 6·8; N, 11·1. $C_{10}H_{16}O_2N_2S_2$ requires C, 46·1; H, 6·2; N, 10·8%).

We thank Dr. E. A. Braude for the determination of absorption spectra.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

[*Received, February 6th*, 1948.]

---

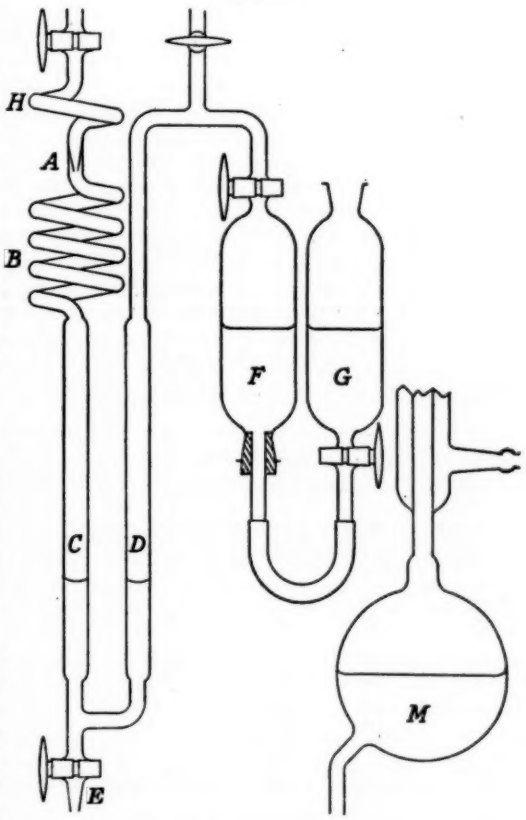
413. *The Measurement of Gas Solubilities.*

By T. J. MORRISON and F. BILLETT.

An apparatus based on the flow of a liquid film through the gas has been developed for the study of gas solubility problems, including the salting-out effect. The method compares favourably with the normal Ostwald technique in rapidity and accuracy.

THE type of apparatus used in most of the work is shown in Fig. 1, though various modifications were tried initially. The thoroughly boiled-out solvent from *M* is injected drop by drop at *A*. The spiral *H* is necessary to preheat the solvent in work at higher temperatures. After flowing through spiral *B*, the liquid passes into the gas burette *C*. The levelling burette *D* is sealed into the bottom of *C*, and saturated solvent is allowed to drop from tap *E* at such a rate that the levels in *C* and *D* are kept the same. Solvent from *E* is collected and measured. Readings of *C* give the volume of gas dissolved, while the volume of solvent is the amount collected at *E* together with the volume accumulating in *C* and *D*. The absorption section is contained in a thermostat. The dimensions are not critical, but a spiral *B* of about 5 turns of 10-mm. tubing with a diameter of about 7 cm. was found suitable; *C* and *D* may be ordinary 50-ml. burette tubes.

FIG. 1.



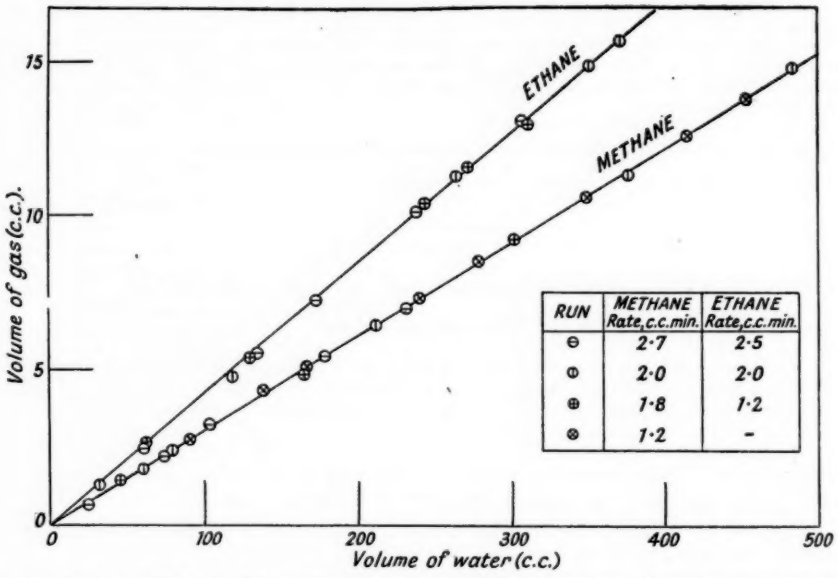
Samples of gas obtained and purified as indicated in the table are stored over saturated water in inverted separating funnels with reservoirs (*F*, *G*). The gas supply is connected to *D* throughout so that constant pressure can be maintained in the absorption section. The absorption apparatus is initially filled with gas either by evacuation or by displacing air-free solvent.

In measuring the solubilities of very soluble gases (with Ostwald coefficients greater than 0·5), the levelling burette *D* is replaced by a second gas burette sealed in above spiral *B*. This contains gas over mercury or saturated solvent, and constant pressure is maintained by adding liquid to the levelling tube of the second burette.

Preliminary work with various modifications of the apparatus established the fact that equilibrium between the film of liquid and gas is attained with considerable rapidity. It was

found that variation in rate of flow within wide limits and in the dimensions of the spiral had no appreciable effect on the solubility. Measurements were carried out with rates as low as

FIG. 2.



0·5 c.c./min. and as high as 5 c.c./min. At low rates, however, the time required for the absorption of sufficient gas becomes too great, and at very high rates the control of the apparatus becomes difficult. There was, however, no indication of any appreciable change in solubility in this range, provided that the drop rate is adjusted to a constant value while readings are being taken. For normal work a range of drop rate from 1·5 to 2·5 c.c./min. was found to be most suitable. A run of 4—6 hours corresponds to agitation for this length of time in the Ostwald method, with the certainty that fresh liquid is continuously exposed to the gas. The method has the marked practical advantage that a number of volume readings can be taken during a run, and the solubility determined graphically from the slope of the line obtained by plotting volume of gas (or burette reading) against volume of liquid. Plots of this type are presented for methane and ethane, on which gases most of the preliminary work was done (Fig. 2). It is also clear that any factor which affects the solubility, such as traces of impurities or incompletely boiled out solvent, will be detected by some curvature of the line. Runs which showed such a curvature were obtained in a few cases and rejected.

DISCUSSION.

The table gives values for the absorption coefficients (calculated from the slopes by reduction to 273° K.) of several gases compared with the recorded values. The values obtained by the

Solvent: water. Temp. 25° ± 0·1°.
(Recorded values from I.C.T.; Seidell, "Solubilities"; and Landolt-Börnstein, "Tabellen.")
Col. ii: rate of flow, c.c./min. Col. iii: absorption coefficient × 10^3. Col. iv: recorded absorption coefficient. Col. v: Deviation, %. Col. vi: method of preparation and purification.

i. Gas.	ii.	iii.	iv.	v.	vi.
CH_4	2·7	27·9	30·1	7	(1) CH_3I and Zn–Cu couple; washed with alcohol and water. (2) CH_3·MgI and H_2O; washed as in (1)
	2·5	27·8			
	2·0	27·9			
	1·8	27·8			
	1·2	27·9			
C_2H_6	1·5 to 2·5	39·1	41·0	5	C_2H_5·MgI and H_2O; washed as for methane
O_2	1·5 to 2·5	28·0	28·3—28·9	1—3	(1) $KMnO_4$ and H_2O_2; washed with water (2) Action of heat on $KMnO_4$
N_2	1·5 to 2·5	14·05	14·3—15·0	2—6	$NaNO_2$ and NH_4Cl; washed with $K_2Cr_2O_7$ and water
C_2H_4	1·5 to 2·5	104·4	108	3	EtOH and H_3PO_4 at 220°; washed with H_2SO_4 and KOH

present method are consistently lower than those got by the Ostwald technique by a few units %. Examination of the literature shows, however, that deviations of this magnitude are not unusual in gas-solubility measurements. It may also be pointed out that the recorded values for the gases used are drawn from relatively old work, and it is suggested that the values obtained by the method described are more reliable because of the absence of any possibility of supersaturation, and possibly because no correction is necessary for change in volume of the solvent. The absence of any type of flexible connection and of stop-cocks in contact with the gas may also contribute to increased reliability. Although these difficulties are realised and overcome in modern applications of the Ostwald technique, yet they may have contributed to somewhat inaccurate results in older investigations. The difficulties experienced in the Ostwald method in bringing gas and solvent into contact without an initial loss due to solution in the upper layer of solvent are also absent. An objection raised by Horiuti (*Sci. Papers Inst. Phys. Chem. Res. Tokio*, **1931—32**, **17**, No. **341**, 168) to the " wet " method (*i.e.*, any method in which the gas is kept saturated with solvent vapour), *viz.*, the possibility of a change in composition when wet gas is transferred from the gas burette to the gas pipette at a different temperature, does not apply in the method described.

Since the method requires the same type of readings as the normal Ostwald method—measurement of a gas volume and of a solvent volume—the accuracy is at least equal to the older method, but confidence in the reliability of the results increases with the number of measurements taken and increasing length of run. We find that results are reproducible within limits of 0·5% and possibly less. The method is therefore presented as an alternative to the Ostwald method, giving at least equal accuracy and requiring rather simpler apparatus.

The thanks of one of us (F. B.) are due to the Hallett Trustees for the award of a Scholarship.

BRIGHTON TECHNICAL COLLEGE. [*Received, February 10th*, 1948.]

---

414. *The Chemistry of Ribose and its Derivatives. Part I. Methyl-D-ribofuranoside and the Characterisation of Trimethyl D-Ribofuranose.*

By G. R. BARKER.

Methyl-D-ribofuranoside has been prepared and its structure confirmed by (*a*) oxidation with sodium metaperiodate and (*b*) methylation and characterisation of trimethyl D-ribofuranose, which yielded the following crystalline compounds: 2 : 3 : 5-*trimethyl* D-*ribose anilide*, 3 : 5-*dimethyl* D-*ribose phenylosazone*, 2 : 3 : 5-*trimethyl* D-*ribonolactone*, and 2 : 3 : 5-*trimethyl* D-*ribonophenylhydrazide*. The natural occurrence of ethyl-D-riboside is discussed.

IN connection with work on ribonucleic acids, the carbohydrate radicals of which have been shown to be of the furanose configuration (Lythgoe and Todd, *J.*, 1944, 592, and references therein), it became necessary to explore methods by which furanose derivatives of ribose could readily be obtained and characterised. Of the various routes which have been used for the synthesis of such compounds the most favourable appears to be that of Levene and Stiller (*J. Biol. Chem.*, **1933**, **102**, 187) who prepared 5-methyl D-ribofuranose and 2 : 3 : 5-trimethyl D-ribofuranose from 2 : 3-*iso*propylidene D-ribofuranose. However, even this method of approach is susceptible of application only to a limited range of compounds. The present paper describes the preparation of *methyl-D-ribofuranoside*, a more generally suitable starting material for syntheses in this field.

Levene and Tipson (*ibid.*, **1931**, **92**, 109) found that D-ribose in methyl alcohol containing 1% of hydrogen chloride exhibited a maximum positive rotation after 14 minutes, and Levene, Raymond, and Dillon (*ibid.*, **1932**, **95**, 699) observed that, under these conditions after one hour, the mixture of glycosides produced contained a small quantity of pyranoside in addition to the furnanoside. In neither of these two series of experiments, however, was an attempt recorded to isolate any product of the condensation. In the present investigations, D-ribose was condensed with methyl alcohol in presence of 1% of hydrogen chloride and the reducing power of the solution was measured by Somogyi's method (*ibid.*, **1926**, **70**, 599) at various intervals of time. After 50 minutes the solution was non-reducing, and the product of the condensation was isolated and distilled under reduced pressure. The furanoside nature of the distillate was suggested by its rapid hydrolysis by dilute mineral acid at 100° and was confirmed by oxidation of the syrup with sodium metaperiodate which produced no formic acid, showing

the presence in the molecule of only two adjacent hydroxyl groups. The identity and homogeneity of the glycoside was established beyond doubt by subjecting it to the following reactions.

Repeated methylation with methyl sulphate yielded 2 : 3 : 5-trimethyl methyl-D-ribofuranoside from which trimethyl D-ribofuranose was obtained by hydrolysis with dilute aqueous mineral acid. The properties of these two syrupy compounds approximated closely to those reported for them by Levene and Stiller (*loc. cit.*) and it was now found possible to characterise the trimethyl D-ribofuranose as its crystalline *anilide* and also to prepare from it 3 : 5-*dimethyl* D-*ribose phenylosazone*. Proof of the structure of the trimethyl D-ribofuranose was obtained by oxidation to crystalline 2 : 3 : 5-*trimethyl* D-*ribonolactone* which gave crystalline 2 : 3 : 5-*trimethyl* D-*ribonophenylhydrazide*. Measurement of the rate of hydrolysis of the lactone in aqueous solution indicated that it was a furanolactone, and hence the trimethyl ribose and the methylriboside must also have possessed the furanose configuration. The crystalline lactone had a higher negative rotation than the compound previously claimed to be 2 : 3 : 5-trimethyl D-ribonolactone (Levene and Tipson, *J. Biol. Chem.*, 1931—32, **94**, 809; Levene and Stiller, *loc. cit.*) but which was neither crystallised nor characterised.

The very rapid formation of the ribofuranoside is of interest in connection with the natural occurrence of the sugar. The only well-authenticated natural derivatives of this sugar are the glycosides of nitrogenous bases concerned in the ribonucleic acids and allied compounds. However, the presence in certain animal tissues of an ethylriboside has been reported (Winter, *Biochem. J.*, 1927, **21**, 467). Winter considered that the ethylriboside may have arisen during the process of extraction from the tissues, but dismissed this possibility on account of the failure of arabinose to yield a glycoside under the conditions employed in the isolation of the alkylriboside. This analogy, however, is not justified since, under similar treatment to that described for ribose in the experimental section, condensation of arabinose takes place much more slowly (Montgomery and Hudson, *J. Amer. Chem. Soc.*, 1937, **59**, 992). The question of the natural occurrence of an ethylriboside, therefore, would need further consideration before it could be regarded as fully established.

Experimental.

Methyl-D-ribofuranoside.—D-Ribose (30 g.), prepared from guanosine following the method of Bredereck, Köthnig, and Berger (*Ber.*, 1940, **73**, 956) and dried in a vacuum over phosphoric oxide at 50°, was dissolved in absolute methyl alcohol (750 c.c.) containing 1% of hydrogen chloride. Samples (0·2 c.c.) were withdrawn and, after neutralisation, analysed by Somogyi's method (*loc. cit.*). After 15 and 30 minutes 82·1% and 94·5%, respectively, of the reducing power of the solution had been lost, and after 50 minutes the solution was non-reducing. It was immediately ground in a mortar with excess of silver oxide, and after standing for 2·5 hours, the silver salts were removed by filtration through charcoal. Distillation below 30° of the solvent gave *methyl-D-ribofuranoside*, as a very hygroscopic syrup, b. p. 150° (bath temp.)/0·01 mm., $n_D^{15°}$ 1·4880, a_D^{15} + 13·1° (in methyl alcohol; *c*, 1·903) (Found : C, 43·6; H, 7·3; OMe, 18·3. $C_6H_{12}O_5$ requires C, 43·9; H, 7·3; OMe, 18·9%). This substance consumed 1·02 mols. of sodium metaperiodate, no formic acid being detected by titration of an aliquot with N/100-sodium hydroxide.

A solution of the substance (0·1903 g.) in N/100-hydrochloric acid (10 c.c.) was heated at 100°, and samples were withdrawn, neutralised with dilute aqueous sodium hydroxide, and analysed by Somogyi's method (*loc. cit.*). After 5 minutes 41·3% of the glycoside had been hydrolysed; after 20 minutes, hydrolysis was complete.

Trimethyl Methyl-D-ribofuranoside.—Methyl-D-ribofuranoside (18 g.) was dissolved in aqueous sodium hydroxide (240 c.c.; 40%) and methylated twice with methyl sulphate (124·5 g.) at 60° during 5 hours. The reaction mixture was heated at 100° for 10 minutes, and after cooling to 0°, sodium sulphate was removed by filtration and the filtrate was extracted four times with chloroform. The combined extracts were dried ($MgSO_4$) and distillation of the solvent yielded trimethyl methyl-D-ribofuranoside, b. p. 133° (bath temp.)/15 mm., $n_D^{15°}$ 1·4350, $a_D^{18°}$ + 59·1° (in methyl alcohol; *c*, 4·784) (Found : C, 52·3; H, 8·3; OMe, 59·7. Calc. for $C_9H_{18}O_5$: C, 52·4; H, 8·73; OMe, 60·2%).

2 : 3 : 5-*Trimethyl* D-*Ribose.*—A solution of trimethyl methyl-D-ribofuranoside (2 g.) in N/25-hydrochloric acid (25 c.c.) was boiled under reflux for 1 hour and cooled, and chloride ions were removed by addition of silver carbonate and filtration. Concentration of the solution under reduced pressure yielded syrupy 2 : 3 : 5-trimethyl D-ribose, b. p. 97° (bath temp.)/0·01 mm., $n_D^{20°}$ 1·4523, $a_D^{24°}$ + 41·4° (in methyl alcohol; *c*, 1·112) (Found : C, 50·2; H, 8·4; OMe, 49·8. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·34; OMe, 48·4%).

2 : 3 : 5-*Trimethyl* D-*Ribose Anilide.*—2 : 3 : 5-Trimethyl D-ribose (0·13 g.) was heated with aniline (0·99 mol.) in absolute alcohol (5 c.c.) for 4 hours. Removal of the solvent in a vacuum desiccator gave the *anilide*, which crystallised on trituration with ether–light petroleum and separated from light petroleum containing a little ether in large rectangular plates and prisms, m. p. 56·5° (Found : C, 63·4; H, 7·8; N, 5·1; OMe, 35·2. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9; N, 5·2; OMe, 35·0%).

3 : 5-*Dimethyl* D-*Ribose Phenylosazone.*—2 : 3 : 5-Trimethyl D-ribose (0·1 g.) was heated at 100° with phenylhydrazine (4 mols.) in dilute acetic acid (5 c.c.) for 4·5 hours. After being cooled to 0°, the crystals were collected and crystallised twice from aqueous alcohol. The *phenylosazone* separated in small yellow needles, m. p. 161° (Found : C, 63·6; H, 7·5; N, 15·3; OMe, 16·3. $C_{19}H_{24}O_3N_4$ requires C, 64·0; H, 6·7; N, 15·7; OMe, 17·3%).

2 : 3 : 5-*Trimethyl* D-*Ribonolactone*.—Trimethyl methyl-D-ribofuranoside (2 g.) was heated at 100° with N/25-hydrobromic acid (25 c.c.) for 1 hour and then allowed to react with bromine (2·5 g.) at 30° for 4 days. The solution, which was then non-reducing, was freed from bromine by aeration, from bromide ions by addition of silver carbonate and filtration, and from silver ions by passage of hydrogen sulphide followed by filtration. Concentration of the filtrate under reduced pressure gave 2 : 3 : 5-*trimethyl* D-*ribonolactone*, b. p. 120° (bath temp.)/0·01 mm., $n_D^{26°}$ 1·4508, which on cooling to 0°, crystallised in needles, m. p. 18·5—19° (Found : C, 50·2; H, 7·9; OMe, 47·7. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4; OMe, 49·0%). The material showed the following rotations in water (*c*, 4·702) : $[\alpha]_D^{23°}$ −20·2° (initial), −18·1° (46 hours), −14·5° (93 hours), −10·6° (141 hours). Levene and Tipson (*loc. cit.*) give $[\alpha]_D^{27°}$ −18·9° (in water, initial value) for syrupy 2 : 3 : 5-trimethyl D-ribonolactone.

2 : 3 : 5-*Trimethyl* D-*Ribonophenylhydrazide*.—2 : 3 : 5-Trimethyl D-ribonolactone (0·05 g.) was heated at 100° with phenylhydrazine (1 mol.) in absolute ethyl alcohol (2 c.c.) for 4 hours. The solvent was allowed to evaporate and the residual 2 : 3 : 5-*trimethyl* D-*ribonophenylhydrazide* then crystallised on being rubbed with dry ether. It separated from ethyl acetate–light petroleum in needles, m. p. 108·5—109·5° (Found : C, 55·8; H, 7·6; N, 9·1. $C_{14}H_{22}O_5N_2$ requires C, 56·4; H, 7·4; N, 9·4%).

The author wishes to record his indebtedness to the late Professor J. Masson Gulland, F.R.S., and Professor E. L. Hirst, F.R.S., for their interest in this work.

THE UNIVERSITY OF MANCHESTER. [*Received, February 13th*, 1948.]

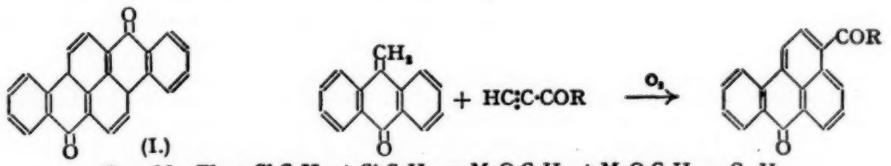
---

415. *A Synthesis of 3-Acyl- and 3-Aroyl-mesobenzanthrones.**

By F. IRVING and A. W. JOHNSON.

3-Acyl- and 3-aroyl-*meso*benzanthrones have been prepared by the reaction of αβ-ethynyl ketones and methyleneanthrone.

3-BENZOYL*meso*BENZANTHRONE is an important dye intermediate, for on cyclisation by heating with aluminium chloride–sodium chloride in the presence of oxygen it yields 1 : 2 : 6 : 7-dibenzpyrene-3 : 8-quinone (Indanthrene Golden Yellow GK; I). It is therefore of interest that a simple method has been found for the preparation of 3-aroyl*meso*benzanthrones which are potential sources of dibenzpyrenequinones substituted in one of the terminal rings. The Diels–Alder reaction of methyleneanthrone and αβ-ethynyl ketones proceeds readily in acetic acid solution on warming to give 3-acyl- and 3-aroyl-*meso*benzanthrones in 50—70% yields, the addition being accompanied by oxidation :



R = Me, Ph, *o*-Cl·C$_6$H$_4$, *p*-Cl·C$_6$H$_4$, *m*-MeO·C$_6$H$_4$, *p*-MeO·C$_6$H$_4$, α-C$_{10}$H$_7$.

The αβ-ethynyl ketones required for the Diels–Alder reactions were prepared by chromic acid oxidation of the corresponding carbinols (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, **39**; Bowden and Jones, *ibid.*, p. 52). The condensation of methyleneanthrone with β-chloropropiophenone (which readily loses hydrogen chloride to give phenyl vinyl ketone) in nitrobenzene solution to give 3-benzoyl*meso*benzanthrone has been described by Allen, Bell, Bell, and van Allan (*J. Amer. Chem. Soc.*, 1940, **62**, 656) although extensions of this method would be restricted by the limited availability of the starting materials.

EXPERIMENTAL.

Preparation of Intermediates.—p-*Methoxyphenylethynylcarbinol*. Purified acetylene was rapidly passed into liquid ammonia (1,000 c.c.) with stirring and cooling, and sodium (23 g.) added in small pieces in such a manner that the blue colour never persisted for more than a few moments. A solution of *p*-methoxybenzaldehyde (redistilled : 136 g.) in ether (100 c.c.) was then added during 1½ hours and the mixture stirred and cooled for a further 3 hours with continued introduction of acetylene. The ammonia was allowed to evaporate overnight, and dilute sulphuric acid (ice) was added to the residue. The product was extracted with ether (3 × 300 c.c.) and the ethereal extracts washed with sodium hydrogen carbonate solution and dried. After removal of the solvent the residue was distilled to yield p-*methoxyphenylethynylcarbinol* (71 g.) as a pale yellow oil, b. p. 146—149°/15 mm. (Found : C, 73·7; H, 6·05. $C_{10}H_{10}O_2$ requires C, 74·05; H, 6·2%). The product readily formed a white insoluble silver derivative.

* Patent application pending.

Since the above work was carried out, Rutan and May (*J. Amer. Chem. Soc.*, 1947, **69**, 2017) have described *p*-methoxyphenylethynylcarbinol as a crystalline solid, m. p. 172—173°. This may be a misprint (phenylethynylcarbinol has m. p. 22°). The sample obtained in the above experiment was oxidised directly to the corresponding ketone and no special effort was made to crystallise it.

p-*Methoxyphenyl ethynyl ketone.* To a stirred solution of *p*-methoxyphenylethynylcarbinol (15·6 g.) in acetone (25 c.c.), a solution of chromium trioxide (8·0 g.) in water (30 c.c.) and concentrated sulphuric acid (7 c.c.) was slowly added. The operation, carried out at 5—10° in nitrogen, lasted 1½ hours. After being stirred for a further 30 minutes, the mixture was diluted with water and the product extracted with ether. Evaporation of the ethereal solution gave a yellow solid which was crystallised from aqueous methanol and then petroleum (b. p. 60—80°) to give p-*methoxyphenyl ethynyl ketone* (9·1 g.) as pale yellow needles, m. p. 82—83° (Found: C, 74·7; H, 4·7. $C_{10}H_8O_2$ requires C, 75·0; H, 5·0%). The ketone readily formed a white insoluble silver derivative and a brick-red insoluble copper derivative.

α-*Naphthyl ethynyl ketone.* α-Naphthylethynylcarbinol was prepared from α-naphthaldehyde (35·6 g.; Badger, *J.*, 1941, 536) by the method described above for *p*-methoxyphenylethynylcarbinol. The crude product (34 g.) was not purified but dissolved in acetone (50 c.c.) and oxidised with a solution of chromium trioxide (18 g.) in water (56 c.c.) and concentrated sulphuric acid (15 c.c.) as described for the preparation of *p*-methoxyphenyl ethynyl ketone. The crude ketone (24 g.) was crystallised from petroleum (b. p. 60—80°) to yield α-*naphthyl ethynyl ketone* as pale yellow plates, m. p. 70—71° (Found: C, 86·25; H, 4·7. $C_{13}H_8O$ requires C, 86·65; H, 4·45%).

Preparation of 3-*Acyl- and* 3-*Aroyl*-meso*benzanthrones.*—3-*Benzoyl*meso*benzanthrone.* Methyleneanthrone (1·3 g.; Clar, *Ber.*, 1936, **69**, 1686) and phenyl ethynyl ketone (1 g.; Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39) were dissolved in acetic acid (6 c.c.) and heated under reflux for ½ hour. The solution at first became dark brown and then lightened until it was finally golden yellow. 3-Benzoyl-*meso*benzanthrone (1·2 g.), m. p. 186—188°, was deposited on cooling and was crystallised from acetic acid, being obtained as bright yellow prisms, m. p. 193—194° (Allen, Bell, Bell, and van Allan, *loc. cit.*, give 192°).

3-*Acetyl*meso*benzanthrone.* Prepared similarly from methyleneanthrone (5 g.) and methyl ethynyl ketone (1·75 g.; Bowden, Heilbron, Jones, and Weedon, *loc. cit.*) in acetic acid (25 c.c.), 3-acetyl*meso*benzanthrone (3·0 g.) formed bright yellow platelets, m. p. 173—175°, from aqueous acetic acid (I.G. Farben., B.P. 440,263, give m. p. 174—175°).

3-p-*Methoxybenzoyl*meso*benzanthrone.* Prepared similarly from methyleneanthrone (3·9 g.) and *p*-methoxyphenyl ethynyl ketone (3·07 g.) in acetic acid (24 c.c.), 3-p-*methoxybenzoyl*meso*benzanthrone* (2·9 g.) formed yellow prisms, m. p. 194—195°, from acetic acid (Found: C, 82·0; H, 4·6. $C_{25}H_{16}O_3$ requires C, 82·4; H, 4·4%).

3-m-*Methoxybenzoyl*meso*benzanthrone.* Prepared similarly from methyleneanthrone (11·1 g.) and *m*-methoxyphenyl ethynyl ketone (8·85 g.; Johnson and Melhuish, *J.*, 1947, 346) in acetic acid (70 c.c.). 3-m-*Methoxybenzoyl*meso*benzanthrone* after crystallisation from acetic acid formed bright yellow prisms (8·85 g.), m. p. 192—193° (Found: C, 82·8; H, 4·7%).

3-o-*Chlorobenzoyl*meso*benzanthrone.* Methyleneanthrone (62·5 g.) and *o*-chlorophenyl ethynyl ketone (50 g., Johnson, *J.*, 1947, 1626) in acetic acid (750 c.c.) were heated on the steam-bath for 1½ hours. The solution at first became dark and then lightened as the dehydrogenation occurred. 3-o-*Chloro-benzoyl*meso*benzanthrone* (49 g.) separated from the solution on cooling and a further quantity (13 g.) was obtained by cautious dilution of the mother liquors. Crystallisation from acetic acid gave the product as yellow prisms, m. p. 206—207° (Found: C, 78·25; H, 3·75. $C_{24}H_{13}O_2Cl$ requires C, 78·2; H, 3·5%).

3-α-*Naphthoyl*meso*benzanthrone.* Prepared similarly from methyleneanthrone (9·1 g.) and α-naphthyl ethynyl ketone (8 g.) in acetic acid (60 c.c.), the product (7·6 g.) was separated and crystallised from chlorobenzene to yield 3-α-naphthoyl*meso*benzanthrone as dark yellow prisms, m. p. 254—255° (I.G. Farben., D.R.-P. 446,187, give m. p. 244—245°) (Found: C, 87·0; H, 4·15. Calc. for $C_{28}H_{16}O_2$: C, 87·5; H, 4·2%). The product dissolved in concentrated sulphuric acid to a cherry-red solution.

IMPERIAL CHEMICAL INDUSTRIES LTD., RESEARCH LABORATORIES,
HEXAGON HOUSE, BLACKLEY, MANCHESTER, 9. [*Received, February 16th*, 1948.]

---

416. *Mechanism of Elimination Reactions. Part VI. Introduction to a Group of Papers. Unimolecular Olefin Formation from* tert.-*Butyl- and* tert.-*Amyl-sulphonium Salts.*

By K. A. COOPER, E. D. HUGHES, C. K. INGOLD, and B. J. MACNULTY.

The plan on which the present papers are arranged is explained. Part VI is concerned with an extension of the range of examples over which the unimolecular mechanism *E*1 of elimination is kinetically demonstrated. Parts VII and VIII extend the study, initiated in Part V (1940), of environmental factors on the bimolecular and unimolecular mechanisms of elimination, *E*2 and *E*1. Parts IX—XVI deal with constitutional factors, a general discussion of which is given in Part XVI.

The mechanisms *E*1 and S_N1 have a common slow stage in which a carbonium ion $\overset{+}{R}$ is formed. It follows that the proportion in which compounds of a series RX, with constant R and variable X, should suffer substitution and elimination by these mechanisms under similar external conditions, should in first approximation be independent of X. In extension of previous work (Parts II—IV), this is verified for R = *tert.*-butyl and for R = *tert.*-amyl, in

each case over the range X = Cl, Br, I, $\overset{+}{S}Me_2$. In the series R = *tert.*-amyl two simultaneous reactions *E*1 occur, producing isomeric olefins. Their proportions should in first approximation be independent of X, and this is confirmed for X = Br, $\overset{+}{S}Me_2$.

Introduction to a Group of Papers.

We here indicate the arrangement of the papers of the present running group, and the directions in which they carry forward the various aspects of the general theme with which the series deals. The first three of these papers constitute additions to branches of the subject that have been treated at some length previously. All the rest belong closely together, and are concerned with the development of an aspect which has hitherto been treated only very incompletely. A short preliminary account of the work was given some years ago (*Trans. Faraday Soc.*, 1941, **37**, 657).

The bimolecular mechanism of elimination (*E*2) was first established as a general mechanism by Hanhart and Ingold in 1927. It was subsequently given a certain amount of kinetic foundation, and this the present group of papers considerably extends. We write the mechanism thus,

$$Y + H\overset{\curvearrowright}{-}CR_2\overset{\curvearrowright}{-}CR_2\overset{\curvearrowright}{-}X \longrightarrow YH + CR_2{=}CR_2 + X \quad . \quad . \quad . \quad . \quad . \quad (E2)$$

introducing the arrows to show the direction of the electron-transfers, but omitting charge-labels in order to imply inclusion of the various possibilities.

The existence of the unimolecular mechanism of elimination (*E*1) was first pointed out by Hughes in 1935. It is formulated thus,

$$\left.\begin{aligned} CHR_2{\cdot}CR_2\overset{\curvearrowright}{-}X &\xrightarrow[\text{slow}]{} CHR_2{\cdot}\overset{+}{C}R_2 + X \\ Y + H\overset{\curvearrowright}{-}CR_2\overset{\curvearrowright}{-}\overset{+}{C}R_2 &\xrightarrow[\text{fast}]{} YH + CR_2{=}CR_2 \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (E1)$$

Once again the charges on X and Y are not indicated as there are various possibilities.

The establishment of this mechanism (*E*1) by kinetic methods was the first task to be taken up when the present series of papers was commenced in 1937. Parts I—IV were concerned with this matter, and the present paper, Part VI, provides an addition to that phase of the general inquiry. We here extend to the reactions of sulphonium salts the use of a method, which in the earlier contributions was applied only to alkyl halides, for confirming the unimolecular mechanism of elimination by the study of product-compositions in kinetically controlled conditions. The generality of the unimolecular mechanism of elimination is kinetically demonstrated over a large range of examples in the other papers of the present group.

Part V of the series, published in 1940, was concerned with various factors which control the facility and relative importance of the bimolecular and unimolecular mechanisms of elimination. It dealt chiefly with what were called environmental factors—reagent, concentration, solvent, and temperature. The next two papers of the present group, Parts VII and VIII of the series, continue this study, inasmuch as they add something to our knowledge of solvent and temperature effects on the two elimination mechanisms.

Our main effort in recent years has, however, been devoted to another branch of the subject, *viz.*, the study of constitutional influences, which, as a matter of fact, was just introduced in Part V. All the remaining papers of the present group develop this theme. Parts IX—XV record various experimental contributions. The main results are brought together, and their theoretical interpretation is considered in Part XVI (this vol., p. 2093).

Unimolecular Olefin Formation from *tert.*-Butyl- and *tert.*-Amyl-sulphonium Salts.

In Part II (*J.*, 1937, 1277) a test of the unimolecular mechanism of elimination, *E*1, was developed on a basis of comparison with the unimolecular mechanism of substitution, S_N1 :

$$\left.\begin{aligned} CHR_2{\cdot}CR_2\overset{\curvearrowright}{-}X &\xrightarrow[\text{slow}]{} CHR_2{\cdot}\overset{+}{C}R_2 + X \\ CHR_2{\cdot}\overset{+}{C}R_2 + Y &\xrightarrow[\text{fast}]{} CHR_2{\cdot}CR_2Y \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (S_N1)$$

The two mechanisms, *E*1 and S_N1, are seen to have a common slow stage. The rapid stages of the two mechanisms differ, but both are reactions of the carbonium ion, from which the group X

has been removed. Therefore if we operate with a series of compounds RX', RX", . . ., containing the same R but a variable X, the specific rate of the total unimolecular reaction

$$k_{\text{heterolysis}} = k_1 = k_{S_N1} + k_{E1}$$

might vary quite largely, but the proportion, k_{E1}/k_1, in which the carbonium ion will decompose in a particular direction should be independent of the nature of X. This is a simplifying overstatement: for stereochemical studies on unimolecular substitution have shown (Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, **1937**, 1257) that, although X must have passed beyond the separation corresponding to the transition state of heterolysis when the fate of $\overset{+}{R}$ is determined, it may not be actually very far away, and therefore could have some influence on the relative rates of the alternative decompositions of $\overset{+}{R}$. However, this effect would be expected to lead to only minor variations in the ratio k_{E1}/k_1, and should certainly not change its order of magnitude; whereas a suitable variation of X might change even the orders of magnitude of the individual rates k_1, k_{S_N1}, and k_{E1}.

The original application of this test, possibly not a very critical one, was to 2-*n*-octyl chloride and bromide, which undergo unimolecular solvolysis in " 60% " aqueous alcohol, giving in part the substitution products, 2-*n*-octyl alcohol and ethyl 2-*n*-octyl ether, and in part the elimination product, octylene. The specific rates of the total solvolytic processes differ by a factor of about 30, but the proportions in which octylene is formed from these two compounds, under the same conditions of solvent and temperature, are the same to within a factor of 1·1. The specific rates of solvolysis were interpreted as the heterolytic rates, k_1, and the olefin proportion as the partition ratio, k_{E1}/k_1, for the decomposition of the separated carbonium ion.

In Part III (*J.*, **1937**, 1280) the same test was applied to the unimolecular solvolysis of the *tert.*-butyl halides. In dilute alkaline, neutral and acidic, " 80% " aqueous alcohol, *tert.*-butyl chloride, bromide, and iodide undergo first order reactions, which are in part substitution and in part elimination:

$$(CH_3)_3CX \longrightarrow \begin{cases} (CH_3)_3C{\cdot}OH \text{ and } (CH_3)_3C{\cdot}OEt \; . \; . \; . \; . \; . \; . & (S_N1) \\ (CH_3)_2C{:}CH_2 \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . & (E1) \end{cases}$$

For this range of substances (X = Cl, Br, I) the specific rates of solvolysis differ by more than 100-fold, but the proportion of olefin remains the same to within a factor of 1·3.

In the same media, dimethyl-*tert.*-butylsulphonium salts also undergo first order solvolytic reactions, which are in part substitution and in part elimination (above formulæ with $X = \overset{+}{S}Me_2$). A direct comparison of the solvolysis rates and product compositions for the reactions of *tert.*-butyl chloride and dimethyl-*tert.*-butylsulphonium chloride under identical conditions has now been carried out. The former series RX (with R = Bu^t) has thus been extended to include the sulphonium ion ($X = \overset{+}{S}Me_2$, Cl, Br, I), with the result that the rates at a common temperature now vary over a range of 1000-fold, whilst the olefin proportions still remain the same to within a factor of 1·3.

In Part IV (*J.*, **1937**, 283) the same method was applied to *tert.*-amyl chloride, bromide, and iodide. In dilute alkaline, neutral, and acidic " 80% " aqueous alcohol, these halides also undergo a first order solvolysis, which is in part a substitution and in part an elimination:

$$\begin{matrix} CH_3{\cdot}CH_2 \\ CH_3 \\ CH_3 \end{matrix}\!\!>\!CX \longrightarrow \begin{cases} CH_3{\cdot}CH_2{\cdot}C(CH_3)_2{\cdot}OH \text{ and } CH_3{\cdot}CH_2{\cdot}C(CH_3)_2{\cdot}OEt \; . \; . \; . & (S_N1) \\ CH_3{\cdot}CH_2{\cdot}C(CH_3){:}CH_2 \text{ and } (CH_3)_2C{:}CH{\cdot}CH_3 \; . \; . \; . \; . & (E1) \end{cases}$$

Here again the solvolysis rates are changed by large factors, whilst the proportions of (total) olefin remain nearly constant.

For the same media, an analogous first-order solvolysis is undergone by dimethyl-*tert.*-amylsulphonium chloride (above formulæ with $X = \overset{+}{S}Me_2$). Accordingly, a comparison has been made of the total solvolysis rates, and of the proportions of total olefin, for the reactions of *tert.*-amyl chloride and dimethyl-*tert.*-amylsulphonium chloride under identical conditions. Thus the previous series RX (with R = *tert.*-amyl) has been extended to include the sulphonium ion ($X = \overset{+}{S}Me_2$, Cl, Br, I), with the result that the rates at a common temperature vary in the extended series over a range of about 500-fold, whilst the olefin proportions remain the same to within a factor of 1·5.

All the above results are included in Table I. They are interpreted as meaning that the solvolytic formation of olefin from the dimethyl-*tert.*-butyl- and -*tert.*-amylsulphonium ion under

the conditions mentioned proceeds by the unimolecular elimination mechanism *E*1, just as it does in the analogous reactions of the *tert.*-butyl and *tert.*-amyl halides.

TABLE I.

Effect of variation of X *on the rate-constant* k_1 (*sec.*$^{-1}$) *and on the rate-ratio* k_{E1}/k_1 *in unimolecular decomposition of* RX.

Solvent.*	Temp.	R.	X.	10^5k_1.	k_{E1}/k_1.	Ref.
60% EtOH	100·0°	2-*n*-Octyl	Cl	0·805	0·13	Part II
			Br	26·8	0·14	
80% EtOH	25·0	*tert.*-Butyl	Cl	0·854	0·168	Part III
			Br	37·2	0·126	
			I	90·1	0·129	
,,	65·3	,,	Cl	89·7	0·363	This paper
			$\overset{+}{S}Me_2$	11·8	0·357	
,,	25·2	*tert.*-Amyl	Cl	1·50	0·333	Part IV
			Br	58·3	0·262	
			I	174	0·260	
,,	50·0	,,	Cl	28·5	0·403	This paper
			$\overset{+}{S}Me_2$	6·66	0·478	

* "*x*% EtOH" means a mixture made from *x* vols. of ethyl alcohol and (100 − *x*) vols. of water.

In the case of the *tert.*-amyl compounds another test of mechanism, similar in general principle to that just described, can be based on the fact that the amylenes produced are mixtures of isomerides. For if they arise by decomposition of a separated carbonium ion, then the proportions in which the isomerides are formed should be nearly independent of the molecule from which the carbonium ion is derived. The necessary comparison of the compositions of the olefin mixtures has been made for those olefins which are formed by unimolecular solvolysis of *tert.*-amyl bromide and dimethyl-*tert.*-amylsulphonium iodide in anhydrous, or nearly anhydrous ethyl alcohol. The determinations were made in connexion with other work, and experimental details will be found in Parts XI and XIV; but those results which are relevant to the present question are cited in Table II. The olefin compositions differ by little more than the experimental error, and their similarity confirms the unimolecular nature of the reactions in which the olefins are formed.

TABLE II.

Effect of variation of X *on the composition of olefin mixtures formed by the decomposition of* RX.

Solvent.	Temp.	R.	X.	$Me_2C{:}CHMe$, %.	$MeEtC{:}CH_2$, %.
100% EtOH.....	25°	*tert.*-Amyl	Br	82	18
97% EtOH.....	24	,,	$\overset{+}{S}Me_2$	87	13

EXPERIMENTAL.

Materials.—Dimethyl-*tert.*-butylsulphonium iodide was prepared as described by Hughes and Ingold (*J.*, 1933, 1571). Dimethyl-*tert.*-amylsulphonium iodide was prepared by allowing freshly decolorised and distilled *tert.*-amyl iodide to combine with dimethyl sulphide in concentrated solution in nitromethane at room temperature. It was crystallised from ethyl alcohol (Found: C, 32·0; H, 6·7; I, 48·8. Calc.: C, 32·3; H, 6·5; I, 48·8%). The iodides in aqueous solution were converted into hydroxides by means of silver oxide, and from the hydroxides the chlorides were prepared by neutralisation with hydrochloric acid. The alcohol–water solvents were made up by volume (cf. Table I, footnote).

Method of Kinetic Measurements.—In all cases the runs were followed by enclosing samples of the original solution at 0° in sealed bulbs, which, after suitable intervals of heating in the thermostat, were quickly cooled with ice–water, and either broken under ice–water when it was intended to estimate the total decomposition, or broken under ice-cold carbon tetrachloride when the purpose was to estimate the olefin. Total decomposition was estimated by titrating the liberated acid with standard alkali using

phenolphthalein as indicator. The olefin was estimated bromometrically as described below. In order to eliminate errors due to the formation of acid and of olefin before the sealed-up mixtures had reached the temperature of the thermostat, pairs of tubes were shaken for two minutes in the thermostat and then used immediately for "initial" estimations of the acid and olefin. The samples used for other estimations were similarly shaken in the thermostat for two minutes, the end of which period was taken as the time-zero.

Methods for Olefin Estimations.—The general methods, with the modifications needed for particular cases, have been described several times before, the most recent account being contained in Part V (*J.*, 1940, 901). We used the extraction technique, but, in the case of the sulphonium salts, we had to introduce a modification in order to eliminate interference from the produced sulphides. The modification consisted of washing the carbon tetrachloride solution (150 c.c.) twice with ice-cold saturated aqueous mercuric chloride (50 c.c.). This removed the sulphides sufficiently well, and caused no detectable loss of amylenes, as was shown by blank experiments. It did produce appreciable losses of butylene, but these were small and regular enough to be compensated by using blank experiments for standardisation, as described before (*loc. cit.*). As Hughes and MacNulty showed (*J.*, 1937, 1283), olefin which is produced in a solution which is also developing acid, tends in due course to disappear owing to hydration; and thus the apparent proportion in which the total reaction leads to olefin at first remains substantially constant and then begins to decrease. Thus the olefin present at a late stage of a run is not a suitable measure of what has been produced; and, on the other hand, measurements of olefin made early in a run are rendered inaccurate by the smallness of the quantity of olefin. The usual procedure was therefore first to carry out a run in which both the acid and the olefin were estimated throughout its course, and then, having from these results selected the range of times most favourable for accurate olefin measurements, to carry out a second run in which most of the tubes employed for olefin estimations were taken out of the thermostat at just one or two times within the favourable period.

Results of Measurements.—The principal results are summarised in Table I. Details of some illustrative runs are given in Table III.

TABLE III.

Illustrating determinations of first-order rate-constants and the proportions of olefin formed in the solvolysis of alkyl halides and sulphonium salts.

(1) *Dimethyl*-tert.-*butylsulphonium Chloride.*—Solvent: "80%" ethyl alcohol. Temperature 65·3°. (*a*) [SMe_2Bu^tCl] initially 0·0640M. Solution initially neutral. In this run the first-order development of acid only was followed, leading to $10^5k_1 = 11{\cdot}8$ sec.$^{-1}$. (*b*) [SMe_2Bu^tCl] initially 0·0643M. Solution initially neutral. Olefin x expressed in c.c. of 0·0675N-thiosulphate per 20 c.c. sample. Comparison is made with the total reaction as calculated for the different times t from the above rate-constant:

t (min.) (corr.)	0·0	20·0	30·0	40·0	50·0	75·0	90·0
x (c.c.) (uncorr.)	2·01	4·42	4·83	5·74	6·46	6·99	8·28
x (c.c.) (corr.)	—	2·41	2·82	3·73	4·45	4·98	6·27
Yield % olefin (corr.)	—	6·3	7·4	9·8	11·65	13·05	16·4
Total reaction %	0·0	13·2	19·2	24·6	34·6	41·2	47·1
Proportion of olefin %	—	(48)	38·5	39·8	33·7	31·7	34·8

(2) tert.-*Butyl Chloride.*—Solvent: "80%" ethyl alcohol. Temperature 65·3°. [Bu^tCl] initially 0·182M. Solution initially neutral. Olefin x expressed in c.c. of 0·0682N-thiosulphate, and acidity y in c.c. of 0·0771N-alkali, each for a 20 c.c. sample:

t (min.) (corr.)	0·0	20·0	30·0	40·0	50·0	60·0	70·0	934·0
x (c.c.) (uncorr.)	1·60	28·04	32·04	34·59	35·60	36·28	35·55	7·56
y (c.c.) (uncorr.)	1·64	31·89	37·91	—	45·03	45·95	46·44	47·17
Proportion of olefin %	—	38·5	37·6	—	34·6	34·6	33·6	7·0

The figures show that hydration of the *iso*butylene becomes appreciable after the first hour.

(3) *Dimethyl*-tert.-*amylsulphonium Chloride.*—Solvent: "80%" ethyl alcohol. Temperature 49·9°. [SMe_2Am^tCl] * initially 0·04608M. Solution initially neutral. Olefin, and the bromine by absorption of which it is measured, are reckoned in c.c. of 0·0492N-thiosulphate, and acidity y is given in c.c. of 0·0406N-alkali, each for a 10 c.c. sample.

t (min.) (corr.)	20	45	75	110	150	200	270	380
y (corr.)	0·80	1·80	2·95	4·00	5·20	6·30	7·50	8·90
10^5k_1 (k_1 in sec.$^{-1}$)	6·12	6·39	6·68	6·58	6·81	6·75	6·67	6·73

The final reading y_∞ was 11·35 c.c. A series of "initial" tubes gave acid production 0·30 c.c., and residual bromine, after its uptake by olefin, 14·10 c.c. (means). A further set of tubes withdrawn from the thermostat 180 mins. later gave acid 6·20 c.c., and residual bromine 9·40 c.c. (means). The proportion of olefin is therefore 47·8%. The comparison experiments on *tert.*-amyl chloride were included in the paper by Hughes and MacNulty (*loc. cit.*).

SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Received, January 15th*, 1948.]

* Am^t = *tert.*-amyl.

417. *Mechanism of Elimination Reactions. Part VII. Solvent Effects on Rates and Product-proportions in Uni- and Bi-molecular Substitution and Elimination Reactions of Alkyl Halides and Sulphonium Salts in Hydroxylic Solvents.*

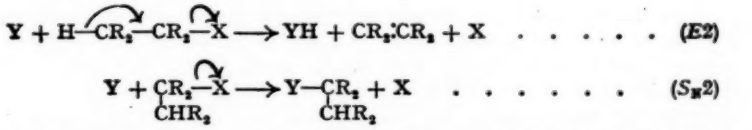
By K. A. Cooper, M. L. Dhar, E. D. Hughes, C. K. Ingold, B. J. MacNulty, and L. I. Woolf.

Consideration is given to the contribution of solvation energy to the activation energy of bimolecular and unimolecular elimination; and a theory is advanced by which it is possible to predict the direction of the effect of a change of solvent on the rate of a bimolecular, or of a unimolecular elimination. By the simultaneous use of a corresponding theory concerning solvent effects on bimolecular and unimolecular nucleophilic substitution, one can forecast the effect of solvent changes on the proportions in which substitutions and eliminations accompany each other.

In confirmation and illustration of these theoretical conclusions, a body of experimental data, some of it new, is assembled concerning solvent effects on the rates and product-proportions of reactions involving elimination. The reactions employed are the acid or alkaline decompositions undergone by alkyl halides and alkylsulphonium salts in water, or ethyl or *n*-propyl alcohol, or mixtures of these solvents.

In 1935 two of us advanced a theory concerning solvent effects in nucleophilic substitution. We have now to state and illustrate a similar theory of solvent effects in olefin eliminations.

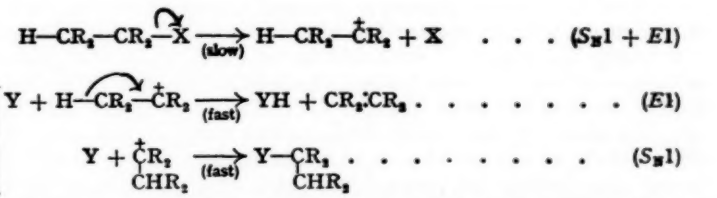
Nucleophilic substitutions and eliminations are so closely parallel in mechanism, and occur so often together, that it is hardly possible to consider one without the other. The bimolecular forms of the two reactions may be represented as follows:



$$Y + H{-}CR_2{-}CR_2{-}X \longrightarrow YH + CR_2{:}CR_2 + X \quad . \quad . \quad . \quad . \quad . \quad (E2)$$

$$Y + \underset{CHR_2}{CR_2}{-}X \longrightarrow Y{-}\underset{CHR_2}{CR_2} + X \quad . \quad . \quad . \quad . \quad . \quad . \quad (S_N2)$$

The electron transfers are similar but pass through a longer chain of atoms in the elimination than in the substitution. The unimolecular forms of the reactions may be expressed as follows:



$$H{-}CR_2{-}CR_2{-}X \xrightarrow[(slow)]{} H{-}CR_2{-}\overset{+}{C}R_2 + X \quad . \quad . \quad . \quad (S_N1 + E1)$$

$$\left\{\begin{array}{l} Y + H{-}CR_2{-}\overset{+}{C}R_2 \xrightarrow[(fast)]{} YH + CR_2{:}CR_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (E1) \\ Y + \underset{CHR_2}{\overset{+}{C}R_2} \xrightarrow[(fast)]{} Y{-}\underset{CHR_2}{CR_2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (S_N1) \end{array}\right.$$

They have a common slow stage and the succeeding fast stages are similar, except that the electron transfer involves a larger number of atoms in the elimination than in the substitution.

Sign-labels have been omitted from the above formulæ because there are several alternatives: the electron transfers alter the state of charge of the atoms involved. Therefore we commence the discussion of solvent effects in elimination, just as we commenced the former discussion of substitutions (*J.*, 1935, 244), by dividing the reactions under consideration into classes, four in all, according to whether the reagent is originally negative becoming finally neutral or is originally neutral becoming finally positive, and, independently, according as the expelled group is initially uncharged becoming ultimately negative, or is initially positive becoming ultimately neutral. The four types are here formulated and exemplified (Ar = p-$NO_2{\cdot}C_6H_4$):

Type 1: $\bar{Y} + H{-}C{-}C{-}X \longrightarrow YH + C{=}C + \bar{X}$

(Example) $\bar{O}H + H{\cdot}CH_2{\cdot}CHMe{\cdot}Br \longrightarrow H_2O + CH_2{:}CHMe + \bar{B}r$

Type 2: $Y + H{-}C{-}C{-}X \longrightarrow \overset{+}{Y}H + C{=}C + \bar{X}$

(Example) $HOEt + H{\cdot}CH_2{\cdot}CMe_2{\cdot}Cl \longrightarrow H_2\overset{+}{O}Et + CH_2{:}CMe_2 + \bar{C}l$

Type 3: $\bar{Y} + H{-}C{-}C{-}\overset{+}{X} \longrightarrow YH + C{=}C + X$

(Example) $\bar{O}Et + H{\cdot}CHMe{\cdot}CMe_2{\cdot}\overset{+}{S}Me_2 \longrightarrow HOEt + CHMe{:}CMe_2 + SMe_2$

Type 4: $Y + H{-}C{-}C{-}\overset{+}{X} \longrightarrow \overset{+}{Y}H + C{=}C + X$

(Example) $H_2O + H{\cdot}CHAr{\cdot}CH_2{\cdot}\overset{+}{N}Me_3 \longrightarrow H_3\overset{+}{O} + CHAr{:}CH_2 + NMe_3$

There are four corresponding types of nucleophilic substitution. It is true of the eliminations and substitutions alike that the similarities between the four types are much more fundamental than their differences; but behaviour with respect to solvent changes, which is our present concern, happens to be one of the main ways in which, for either reaction, the four types differ.

All four types of elimination may proceed by the bimolecular mechanism $E2$. When we discuss solvent influence on this mechanism we shall be considering directly the effect on rate of bimolecular olefin formation. If we should wish to discuss the effect of solvent changes on the proportion in which the total bimolecular reaction yields olefin, it would be necessary to apply a parallel consideration to the corresponding bimolecular substitution S_N2, and make a comparison of the results.

The four types of elimination may also proceed by the unimolecular mechanism ($E1$). However, this and the unimolecular substitution mechanism (S_N1) have a common rate-determining stage, and it is therefore convenient to deal first with the effect of solvent changes on the rate of this stage, *i.e.*, on the rate of the total unimolecular reaction $S_N1 + E1$. Only two cases arise for consideration, because reactions of Types 1 and 2 are identical in form, and reactions of Types 3 and 4 are similarly identical, with respect to the rate-controlling stage of the unimolecular process. If we should seek the solvent effect on the proportion in which the total unimolecular reaction produces olefin, it would be necessary to compare the predicted solvent effects on the rates of the final rapid stages of the unimolecular mechanisms $E1$ and S_N1. Here again only two cases arise, because reactions of Types 1 and 3 are of the same form, and reactions of Types 2 and 4 are also of the same form, with respect to the rapid stages of the unimolecular processes.

The theory which we employ for the discussion of solvent effects is based on the simple picture of an ionising solvent as one whose molecules are attracted to electrically charged centres, and thus, by doing electrostatic work, reduce the energy of the system. Because of its intense local electric fields, water does this *par excellence*; and it is followed, in order of diminishing effectiveness, by the simpler alcohols, aprotic dipolar solvents, and non-polar solvents; *e.g.*, $H_2O > EtOH > Me_2CO > C_6H_6$.

The argument by which we deduce the effect of solvent changes on olefin elimination is similar to that previously applied to nucleophilic substitution. The effect of solvation on the rate of each activated process is assumed to arise from the difference between the solvation energy of the transition state and that of the initial state. The following postulates are made concerning the degree of solvation to be expected in the presence of electric charges: (1) solvation will increase with the magnitude of the charge; (2) solvation will decrease with increasing distribution of a given charge; (3) the decrease of solvation due to distribution will be less than the decrease due to destruction of the same amount of charge. By applying these rules differentially to the initial and transition states, we can deduce the effect of solvation on the energy of activation and hence on the rate. The direction of the effect being thus determined, we know that its magnitude will be greater the more ionising the solvent. The influence of entropy is here neglected, since it appears to be small in comparison with the energy effect of solvation. From a quantitative point of view this is a fault; but our theory could scarcely be elevated to a quantitative status without a much more detailed knowledge of solvation than we at present possess.

The application of these arguments to the bimolecular reactions is indicated in Table I. What happens to the charges on activation is shown in the middle three columns of the Table. The conclusions concerning the rates of bimolecular substitution and elimination (S_N2 and $E2$) are in the last column but one. It will be noted that the solvent effect on rate is always qualitatively the same for bimolecular substitutions and eliminations of the same type. The strong differences are those which occur between the types. The terms "large" and "small" are purely relative: they arise from the theory that the effect of the dispersal of a charge should be notably smaller than the effect of the creation or destruction of a charge (postulate 3 above).

In order to deduce the direction of the solvent effect on the proportions in which these bimolecular reactions produce olefin, it is necessary to be able to compare the qualitatively similar effects on the competing substitutions and eliminations. This we cannot do for those cases in which charges are created or destroyed by activation, since we have no means of comparing the amounts of charge created or destroyed by the two competing processes. But in those cases in which charges are dispersed, we can plausibly assume that they are more

extensively dispersed in the transition state of elimination than in that of substitution. Thus we reach the conclusions indicated in the last column of Table I.

TABLE I.

Predicted solvent effects on the rates and proportions of bimolecular substitutions and eliminations (S_N2 *and* E2).

Type.	Reaction.	Disposition of charges. Initial state.	Disposition of charges. Transition state.	Effect of activation on charges.	Effect of ionising medium on reaction rates.	Effect of ionising medium on olefin proportion.
1	S_N2	$\bar{Y} + RX$	$\overset{\delta-}{Y}\ldots R\ldots \overset{\delta-}{X}$	Dispersed	Small decrease	Small decrease
	$E2$	,,	$\overset{\delta-}{Y}\ldots H\ldots C\cdots C\ldots \overset{\delta-}{X}$			
2	S_N2	$Y + RX$	$\overset{\delta+}{Y}\ldots R\ldots \overset{\delta-}{X}$	Increased	Large increase	?
	$E2$	,,	$\overset{\delta+}{Y}\ldots H\ldots C\cdots C\ldots \overset{\delta-}{X}$			
3	S_N2	$\bar{Y} + R\overset{+}{X}$	$\overset{\delta-}{Y}\ldots R\ldots \overset{\delta+}{X}$	Reduced	Large decrease	?
	$E2$	,,	$\overset{\delta-}{Y}\ldots H\ldots C\cdots C\ldots \overset{\delta+}{X}$			
4	S_N2	$Y + R\overset{+}{X}$	$\overset{\delta+}{Y}\ldots R\ldots \overset{\delta+}{X}$	Dispersed	Small decrease	Small decrease
	$E2$	,,	$\overset{\delta+}{Y}\ldots H\ldots C\cdots C\ldots \overset{\delta+}{X}$			

The corresponding argument for unimolecular reactions is given in Table II. The upper part of the Table is concerned with solvent effects on rates of total unimolecular processes, substitution plus elimination. These are the rates which measure the slow stage which is

TABLE II.

Predicted solvent effects on the rates and proportions of unimolecular substitutions and eliminations (S_N1 *and* E1).

Type.	Reaction.	Disposition of charges. Initial state.	Disposition of charges. Transition. state.	Effect of activation on charges.	Effect of ionising medium on reaction rates.	Effect of ionising medium on olefin proportion.
			Effect on total rate.			
1, 2	$S_N1 + E1$	RX	$\overset{\delta+}{R}\ldots\ldots \overset{\delta-}{X}$	Increased	Large increase	See below
3, 4	$S_N1 + E1$	$R\overset{+}{X}$	$\overset{\delta+}{R}\ldots\ldots \overset{\delta+}{X}$	Dispersed	Small decrease	See below
			Effect on olefin proportion.			
1	S_N1	$\bar{Y} + \overset{+}{R}$	$\overset{\delta-}{Y}\ldots\ldots \overset{\delta+}{R}$	Reduced	Large decrease	?
3	$E1$	,,	$\overset{\delta-}{Y}\ldots H\ldots C\cdots \overset{\delta+}{C}$	,,		
2	S_N1	$Y + \overset{+}{R}$	$\overset{\delta+}{Y}\ldots\ldots \overset{\delta+}{R}$	Dispersed	Small decrease	Small decrease
4	$E1$	,,	$\overset{\delta+}{Y}\ldots H\ldots C\cdots \overset{\delta+}{C}$	,,		

common to unimolecular substitution and elimination; and accordingly, the transition states of which we have here to take account are those of the slow initial stages of these reactions. The lower part of the Table deals with solvent effects on the proportions in which olefin is produced in these unimolecular reactions. The proportions are determined by the relative

rates of the competing fast stages of unimolecular substitution and elimination, and the relevant transition states are therefore those of the fast stages. We are unable to verify the predicted solvent effects of these fast reactions individually, but the relative effects on the competing process determine the effect on the proportion of olefin.

We shall now compare these theoretical expectations with experiment, using our measurements on the rates and product compositions of the reactions of various alkyl halides and sulphonium salts in acid or alkaline ethyl alcohol–water mixtures. In applying the theory we, of course, take water to be the more ionising solvent constituent.

The data for the rates of bimolecular reactions are assembled in Table III. The reactions of Types 1 and 3 are proved to be bimolecular by their kinetic order; and the constants tabulated are second-order rate constants. The reactions of Types 2 and 4 are solvolytic in

TABLE III.

Observed solvent effects on the rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*; k_1 *in sec.*$^{-1}$) *of the bimolecular substitutions and eliminations* (S_N2 *and* E2) *in aqueous ethyl alcohol.*

Type.	Rctn.	Example.	Rate const.	Temp.	Vol. % H_2O in aqueous EtOH.						Predicted effect.
					0.	10.	20.	30.	40.	100.	
1[a]	S_N2	$Pr^iBr + \bar{O}H$	10^4k_2	55°	0·60	—	0·49	—	0·30	—	Small decr.
	E2	,,	,,	,,	1·46	—	0·71	—	0·47	—	,,
2[a]	S_N2	$Pr^iBr + H_2O$	10^5k_1	,,	0·0173	—	0·236	—	0·667	—	Large incr.
3[b]	S_N2	$Me_3\overset{+}{S} + \bar{O}H$	10^4k_2	100	7240	—	178	—	15·1	0·369	Large decr.
	E2	$Et_3\overset{+}{S} + \bar{O}H$	,,	,,	—	—	205	—	21·0	0·242	,,
4[c]	E2	$Ar\cdot[CH_2]_2\cdot\overset{+}{N}Me_3 + H_2O$	10^5k_1	,,	—	20·95	—	13·96	—	3·88	Small decr.

(*a*) Hughes, Ingold, and Shapiro, *J.*, 1936, 255; Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 899.
(*b*) Gleave, Hughes, and Ingold, *J.*, 1935, 236.
(*c*) (Ar = p-$NO_2\cdot C_6H_4$) Hughes and Ingold, *J.*, 1933, 523. The alcoholic constituent of the solvent was *n*-propyl alcohol in this case.

character, and the tabulated constants are therefore first-order constants; but the reactions are believed to be essentially bimolecular, largely on account of the sensitivity of the rates to added bases. In the last column of the table the qualitative predictions are recapitulated for comparison with the figures. It will be noted that the effects are always in the expected directions. Furthermore, corresponding to the predicted distinction between " large " and " small " effects, there is a clear difference in the orders of magnitude of the effects observed. " Large " effects are illustrated by figures which indicate rate ratios for pure ethyl alcohol and pure water * of orders such as $10^4 : 1$ or $1 : 10^3$; whereas " small " effects are represented by data indicating ratios in the two pure solvents of the order of 10 : 1 only.

Some figures for the rates of unimolecular reactions are given in Table IV. Here we have only two distinct reaction types, but their solvent effects differ strikingly in both direction and magnitude. Once again there is good agreement with qualitative theoretical prediction.

In Table V we present the evidence concerning the effect of solvent composition on the proportions of olefin produced from alkyl halides and sulphonium ions by reactions of those molecularities and types which have been studied in aqueous ethyl alcohol. The universal rule appears to be a moderate drop in the proportion of olefin as the solvent becomes more aqueous. This agrees with the theoretical predictions, where these are definite. In the case in which no prediction is made, the theoretical interpretation of the observed result would be that the loss of charge in the formation of the transition state is at least not smaller when the anion is attacking hydrogen than when it is attacking carbon.

* These calculations can readily be made with the aid of Olson and Halford's formula (cf. Bird, Hughes, and Ingold, *J.*, 1943, 255, and papers there cited).

TABLE IV.

Observed solvent effects on the rate-constants (10^5k_1 *with* k_1 *in sec.*$^{-1}$) *of unimolecular substitutions and eliminations* (S_N1 *and* E1) *in aqueous ethyl alcohol.*

Type.	Rctn.	Example.	Temp.	Vol. % H_2O in aqueous EtOH.								Predicted effect.
				0.	10.	20.	30.	40.	50.	60.	100.	
1 & 2	S_N1 + $E1$	Bu^tCl[a]	25°	—	0·171	0·914	4·03	12·6	36·7	129·4	—	Large increase
		Bu^tBr[b]	25	0·45	—	37·0	—	—	—	—	—	
		,, [c]	55	19·8	—	1320	—	—	—	—	—	
		Am^tCl[d]	25	—	—	1·45	—	14·8	—	—	—	
		Am^tBr[e]	25	1·09	—	58·2	—	—	—	—	—	
3 & 4	S_N1 + $E1$	$\overset{+}{S}Me_2Bu^t$[f]	50	1·78	—	1·24	—	—	—	—	0·60	Small decrease
		,,	80	—	—	89·7	—	—	—	—	43·9	
		$\overset{+}{S}Me_2Am^t$[g]	50	15·0	—	6·66	—	—	—	—	—	
		,,	65·3	—	—	61·8	—	—	45·3	—	—	

(*a*) Hughes, *J.*, 1935, 255.
(*b*) Cooper and Hughes, *J.*, 1937, 1183; Cooper, Hughes, and Ingold, *J.*, 1937, 1280; cf. Part XI.
(*c*) Cooper and Hughes, *loc. cit.*; Hughes, Ingold, Masterman, and MacNulty, *loc. cit.*
(*d*) (Am^t = *tert.*-amyl) Hughes and MacNulty, J., 1937, 1283.
(*e*) *Idem. ibid.*, cf. Part XI.
(*f*) Cf. Parts VIII and XIV. The figure 1·78 for 10^5k_1 refers to EtOH with 3% H_2O. The figures 1·24 and 0·60 are calculated from measurements at other temperatures.
(*g*) Cf. Parts V, VIII, and XIV. The figure 15·0 for 10^5k_1 refers to EtOH containing 3% H_2O.

TABLE V.

Observed solvent effects on the proportion of olefin (*expressed below as a percentage of the total decomposition*) *in bi- and uni-molecular reactions* (*substitution plus elimination*) *in aqueous ethyl alcohol.*

Type.	Reaction.	Example.	Temp.	% H_2O in aqueous EtOH.				Predicted effect.
				0.	20.	40.	100.	
1	$S_N2 + E2$	$Pr^iBr + \bar{O}H$[a]	55°	71	59	54	—	Small decr.
2	$S_N1 + E1$	Bu^tBr[b]	25	19·0	12·6	—	—	Small decr.
		Am^tCl[c]	,,	—	33·0	25·7	—	
		Am^tBr[d]	,,	36·3	26·2	—	—	
3	$S_N2 + E2$	$\overset{+}{S}Et_3 + \bar{O}H$[e]	100	—	100	100	86	?
4	$S_N1 + E1$	$\overset{+}{S}Me_2Am^t$[f]	50	64·4	47·8	—	—	Small decr.
		,,	65·3	—	49·4	39·8[g]	—	

(*a*) See Table III, footnote *a*.
(*b*) ,, ,, IV, ,, *b*.
(*c*) ,, ,, ,, ,, ,, *d*.
(*d*) See Table IV, footnote *e*.
(*e*) ,, ,, III, ,, *b*.
(*f*) ,, ,, IV, ,, *g*.
(*g*) The figure 39·8% is interpolated.

EXPERIMENTAL.

The methods used for the preparation of dimethyl-*tert.*-butyl- and -*tert.*-amyl-sulphonium salts, for following the kinetics of their hydrolysis or alcoholysis, and for estimating the production of olefin, were as described in Part VI. The main numerical results are included in the preceding Tables. Details of some of the experiments are given in Table VI. Other experiments are described in the accompanying papers, Parts VI, VIII, XI, and XIV.

TABLE VI.

*Illustrating determinations of rates of solvolysis of dimethyl-*tert.*-butyl- and -tert.-amyl-sulphonium ion in water and aqueous ethyl alcohol.*

(*a*) Solvent: water. Temp.: 80·1°. [SMe_2Bu^tCl] initially 0·0593M. Solution initially neutral. Acidity, y, at time t, recorded in c.c. of 0·0592N-alkali per 10 c.c. sample. Mean $k_1 = 43{\cdot}9 \times 10^{-5}$ sec.$^{-1}$.

t (min.) (uncorr.)	0·0	5·5	10·0	14·8	20·0	25·05
y (uncorr.)	0·43	1·70	2·64	3·53	4·32	5·09
10^5k_1 (k_1 in sec.$^{-1}$)	—	43·1	43·6	43·9	43·4	44·2
t (min.) (uncorr.)	30·05	39·0	49·0	65·0	90·0	128·2
y (uncorr.)	5·69	6·60	7·47	8·32	9·11	9·69
10^5k_1 (k_1 in sec.$^{-1}$)	44·3	44·2	45·0	44·5	43·7	42·0

(*b*) Solvent: " 80% EtOH ", *i.e.*, a mixture of 4 vols. anhydrous ethyl alcohol with 1 vol. water. Temp. 80·1°. [SMe_2Bu^tCl] initially 0·0637M. Solution initially neutral. Development of acidity, y, recorded in c.c. of 0·0500N-alkali per 10 c.c. sample. Mean $k_1 = 89{\cdot}7 \times 10^{-5}$ sec.$^{-1}$.

t (min.) (uncorr.)	0·0	5·05	8·00	14·5	17·5
y (uncorr.)	1·03	3·74	5·07	6·41	7·44
10^5k_1 (k_1 in sec.$^{-1}$)	—	86·6	88·2	89·2	90·9
t (min.) (uncorr.)	17·5	23·0	29·0	35·5	47·0
y (uncorr.)	8·19	9·44	10·26	11·05	11·65
10^5k_1 (k_1 in sec.$^{-1}$)	89·9	91·6	86·4	92·0	—

(*c*) Solvent: " 50% EtOH ", *i.e.*, a mixture of equal volumes of anhydrous ethyl alcohol and water. Temp. 65·3°. [SMe_2Am^tCl] initially 0·05533M. Solution initially neutral. Acidity, y, at time t, recorded in c.c. of 0·0477N-alkali, and bromine, x, after absorption of part of it by olefin, in c.c. of 0·0492N-thiosulphate, each per 10 c.c. sample. Mean $k_1 = 44{\cdot}6 \times 10^{-5}$ sec.$^{-1}$.

t (min.) (corr.)	10·0	20·0	30·0	40·0	∞
y (corr.)	2·6	4·6	5·9	7·2	11·6
10^5k_1 (k_1 in sec.$^{-1}$)	45·0	45·7	42·7	45·1	—
t (min.) (uncorr.)	0·0	0·0	0·0	20·0	20·0
y (uncorr.)	0·60	0·60	—	5·10	5·10
x (uncorr.)	13·85	13·9	13·95	10·85	10·60
[HCl] (units of y)	0·0	0·0	0·0	4·5	4·5
[Olefin] (units of x)	0·0	0·0	0·0	3·05	3·30
t (min.) (uncorr.)	20·0	20·0	40·0	40·0	40·0
y (uncorr.)	—	—	7·80	7·80	—
x (uncorr.)	10·90	10·80	9·90	10·00	9·66
[HCl] (units of y)	—	—	7·1	7·1	—
[Olefin] (units of x)	3·00	3·06	4·00	3·90	4·24

The mean proportion of olefin at $t = 20$ min. is 35·3%. The mean at $t = 40$ min. is lower, 28·4%, showing the incursion of olefin hydration.

(*d*) Solvent: " 50% EtOH ". Temp. 65·3°. [SMe_2Am^tCl] initially 0·1042M. Solution initially neutral. Acidity, y, at time t, expressed in c.c. of 0·1059N-alkali per 10 c.c. sample. Mean $k_1 = 45{\cdot}7 \times 10^{-5}$ sec.$^{-1}$.

t (min.) (corr.)	5·0	10·0	15·0	20·0	30·0
y (corr.)	1·22	2·43	3·29	4·20	5·50
10^5k_1 (k_1 in sec.$^{-1}$)	44·5	47·9	45·9	47·1	46·3
t (min.) (corr.)	40·0	63·0	90·0	246	∞
y (corr.)	6·49	7·95	8·97	9·73	9·74
10^5k_1 (k_1 in sec.$^{-1}$)	45·8	44·9	43·4	—	—

(*e*) Solvent: " 50% EtOH ". Temp. 65·3°. [SMe_2Am^tCl] initially 0·1182M. Solution initially neutral. Units of y and t as for expt. (*d*). Mean $k_1 = 45{\cdot}8 \times 10^{-5}$ sec.$^{-1}$.

t (min.) (corr.)	10·0	16·0	22·0	30·0	∞
y (corr.)	2·14	4·01	4·98	6·24	11·17
10^5k_1 (k_1 in sec.$^{-1}$)	46·9	46·3	44·7	45·5	—

(*f*) Solvent: " 80% EtOH " (cf. expt. *b*). Temp. 65·3°. [SMe_2Am^tCl] initially 0·04425M. Solution initially neutral. Acidity, y, at time t, expressed in c.c. of 0·0406N-alkali, and residual bromine, x, after the uptake of part of it by the olefin, in c.c. of 0·0492N-thiosulphate, each per 10 c.c. sample. Mean $k_1 = 60{\cdot}3 \times 10^{-5}$ sec.$^{-1}$.

t (min.) (corr.)	5·0	10·0	15·0	20·0	24·0
y (corr.)	1·75	3·30	4·50	5·50	6·35
10^5k_1 (k_1 in sec.$^{-1}$)	—	60·1	59·2	58·5	60·7

TABLE VI (*continued*).

t (min.) (corr.)	30·0	35·0	40·0	60·0	100·0
y (corr.)	7·30	7·85	8·40	9·65	10·25
10^5k_1 (k_1 in sec.$^{-1}$)	61·6	60·6	61·0	60·1	—

Determined as in expt. *c*, the mean proportion of olefin at $t = 20$ min. was 48·5%. The mean at $t = 60$ min. was 40·0%, showing the incursion of olefin hydration.

(*g*) Solvent: "80% EtOH". Temp. 65·3°. [SMe_2Am^tCl] initially 0·02471M. Solution initially neutral. Mean $k_1 = 65·8 \times 10^{-5}$ sec.$^{-1}$. Mean proportion of olefin = 50·3%.

(*h*) Solvent: "80% EtOH". Temp. 65·3°. [SMe_2Am^tCl] initially 0·1250M. Solution initially neutral. Mean $k_1 = 59·5 \times 10^{-5}$ sec.$^{-1}$.

SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Received, January 15th*, 1948.]

---

418. *Mechanism of Elimination Reactions. Part VIII. Temperature Effects on Rates and Product-proportions in Uni- and Bi-molecular Substitution and Elimination Reactions of Alkyl Halides and Sulphonium Salts in Hydroxylic Solvents.*

By K. A. COOPER, E. D. HUGHES, C. K. INGOLD, G. A. MAW, and B. J. MACNULTY.

A survey is made of the available data, including some new results, concerning temperature effects on rates and product-proportions in bi- and uni-molecular eliminations, and the accompanying nucleophilic substitutions, of alkyl halides and alkylsulphonium salts. The data are analysed in terms of the parameters of the Arrhenius equation, and the main regularities are pointed out. One is that, in both bi- and uni-molecular reactions of both alkyl halides and alkylsulphonium salts, the Arrhenius activation energy of elimination is higher than that of the accompanying substitution of the same molecularity. Another is that the substitutions and eliminations of organic ions have larger Arrhenius activation energies, and larger frequency factors, than do the corresponding reactions of neutral molecules; and that this effect of ionic character in the reactant is particularly marked for unimolecular reactions.

These relations may be consistently interpreted on the hypothesis that the differences of activation energy are largely due to differences of solvation energy, which can be theoretically treated as explained in the preceding paper. In the comparisons between simultaneous substitutions and eliminations the main distinction of theoretical importance relates to the solvation of the transition states of these processes. In the comparison between charged and neutral reactants, the emphasis is on the difference of solvation of the initial states. By a straightforward extension of the theory, it is possible to deal with the complementary question of the effect of solvation entropy on the frequency factors of the reactions compared.

WE here report some new measurements on the temperature coefficients of reactions which are undergone in hydroxylic solvents by alkyl halides and sulphonium salts in conditions leading to the substantial formation of olefins. It is interesting to set the new data beside previous results of the same nature, and to treat the whole in relation to our division of nucleophilic substitutions and eliminations each into four types distinguished by charge distribution (preceding paper), and in relation to the two mechanisms, the bi- and the uni-molecular, which in principle are available to each of the four types.

(1) *Survey of the Observations.*—We shall first discuss the bimolecular decompositions. Since they are one-stage processes, we have to consider directly, and in the first instance separately, the temperature coefficients of the rates of the simultaneous bimolecular reactions of substitution and elimination, S_N2 and $E2$. If the temperature coefficients are different, then the difference will be reflected in the fact that the proportion in which the total bimolecular reaction produces olefin will shift as the temperature changes.

For the purpose of expressing the dependence of the rates on temperature, we use the Arrhenius equation, $k_2 = B_2e^{-E/RT}$, where k_2 is the second-order rate constant. The known values of B_2 (in sec^{-1} g.-mol.$^{-1}$ l.) and E (in kilocals./g.-mol.) for bimolecular eliminations, and the bimolecular nucleophilic substitutions which accompany them, are given in Table I.

These data enable us to state that, so far as is known, the rates of the second-order eliminations which simple alkyl chlorides, bromides, and iodides undergo in aqueous and alcoholic solvents all have temperature coefficients corresponding to Arrhenius energies of activation * contained in the range 20—25 kilocals./g.-mol. The range for the second-order

* In the case of the substitutions it is known that the Arrhenius energies of activation can be markedly changed by steric hindrance (Dostrovsky and Hughes, *J.*, 1946, 157).

TABLE I.

Arrhenius parameters for bimolecular elimination and the accompanying substitution reactions (S_N2 and E2) in aqueous alcohol.

Type.	Example.	Solvent.[a]	Substitution.		Elimination.	
			$\log_{10} B_2$.	E.	$\log_{10} B_2$.	E.
1[b]	$Pr^iBr + \bar{O}R$	"60% EtOH"	9·4	20·8	10·4	22·1
	$Pr^iI + \bar{O}R$	"	9·7	20·7	11·1	22·2
	$Pr^iCl + \bar{O}R$	"80% EtOH"	9·4	23·1	10·7	24·8
	$Pr^iBr + \bar{O}R$	"	10·1	21·7	10·9	22·6
	$Bu^tBr + \bar{O}R$	"100% EtOH"	—	—	10·1	19·7
3[c]	$\overset{+}{S}Me_2Bu^t + \bar{O}R$	"100% EtOH"	—	—	14·9	24·0
	$\overset{+}{S}Me_2{\cdot}[CH_2]_2{\cdot}Ph + \bar{O}R$	"	—	—	15·0	23·9
	$\overset{+}{S}Me_2{\cdot}CHMePh + \bar{O}R$	"	—	—	16·0	26·2

(*a*) "*x*% EtOH" means a mixture of *x* vols. of anhydrous ethyl alcohol with 100 − *x* vols. of water. (*b*) Hughes, Ingold, and Shapiro, *J.*, 1936, 225; Hughes and Shapiro, *J.*, 1937, 1177; Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 899; Dhar, Hughes, and Ingold, Part XI, this vol., p. 2065.

(*c*) Cf. Parts XII and XIII. The figures for $\overset{+}{S}Me_2{\cdot}CHMePh$ refer to a total reaction containing 40% of substitution and 60% of elimination.

elimination reactions of alkylsulphonium ions seems to lie somewhat higher, *viz.*, 24—26 kilocals./g.-mol. However, for any given pair of simultaneous bimolecular processes, the elimination has, in each of the investigated cases, an Arrhenius energy of activation which lies higher than that of the accompanying substitution by 1—2 kilocals./g.-mol. The elimination thus has always the larger temperature coefficient, so that a rise of temperature increases the proportions in which olefin is formed. This effect of temperature on the bimolecular reactions is illustrated in Table II.*

TABLE II.

Variation with temperature of the proportions in which olefins are formed in bimolecular substitution and elimination (S_N2 and E2).

Solvent: "60% EtOH".[a]			Solvent: "80% EtOH".[a]			Solvent: "100% EtOH".[b]		
Reaction.	Temp.	% Olefin.	Reaction.	Temp.	% Olefin.	Reaction.	Temp.	% Olefin.
$Pr^iBr + \bar{O}R$	45°	53·2	$Pr^iCl + \bar{O}R$	70°	57·1	$Et\overset{+}{S}Me_2 + \bar{O}R$	45°	12·0
"	75	57·5	"	90	60·6	"	64	15·4
"	100	63·6	$Pr^iBr + \bar{O}R$	50	58·1	$Pr^i\overset{+}{S}Me_2 + \bar{O}R$	45	60·6
$Pr^iI + \bar{O}R$	50	69·8	"	80	61·2	"	64	65·7
"	70	72·7	"	100	66·5			

(*a*) See Table I, footnotes *a* and *b*. (*b*) See Table I, footnotes *a* and *c*.

We shall now review the unimolecular reactions. They involve two stages, of which the first is rate-determining. Simultaneous substitution and elimination reactions of the same alkyl compound will have a common slow stage, *viz.*, the heterolysis of the alkyl compound: and

* The substitutions with which the eliminations from sulphonium ions are in competition are themselves composite processes, since alternative alkyl groups can be displaced by substitution (cf. Parts XII, XIII, and XIV).

the rate of this process is the measured rate of the total unimolecular reactions, $S_N1 + E1$. Since this total rate thus has a simple mechanistic significance, it is natural to consider its temperature-dependence before discussing the temperature-variation of the rates of the separate reactions, S_N1 and $E1$.

Again we employ the Arrhenius equation $k_1 = B_1e^{-E/RT}$, where k_1 is now the first-order rate constant of the total unimolecular reaction. Table III contains the value of B_1 (in sec.$^{-1}$) and E (in kilocals./g.-mol.) for those unimolecular reactions in hydroxylic solvents which alkyl halides and sulphonium ions undergo giving known proportions of olefin.

TABLE III.

Arrhenius parameters for total unimolecular reactions involving both substitution and elimination ($S_N1 + E1$) *in hydroxylic solvents.*

Type.	Example.	Solvent.[a]	Total reaction. $\log_{10} B_1$.	Total reaction. E.
2	Bu^tCl solvolysis[b]	"50% EtOH"	13·4	22·9
	Bu^tCl ,,	"80% EtOH"	11·9	23·2
	Bu^tBr ,, [c]	,,	13·3	22·8
	Bu^tI ,, [c]	,,	13·4	22·4
	Am^tCl ,, [d]	,,	11·9	22·9
	Bu^tBr ,, [e]	"100% EtOH"	12·7	24·6
4	$\overset{+}{S}Me_2Bu^t$,,	Water	17·1	33·0
	$\overset{+}{S}Me_2Bu^t$,,	"80% EtOH"	17·2	32·7
	$\overset{+}{S}Me_2Am^t$,,	,,	17·2	31·6

(*a*) Cf. Table I, footnote *a*.
(*b*) Hughes, *J.*, 1935, 255.
(*c*) Cooper and Hughes, *J.*, 1937, 1183.
(*d*) (Am^t = *tert.*-amyl) Hughes and MacNulty, *J.*, 1937, 1283.
(*e*) Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 899; Dhar, Hughes, and Ingold, Part XI, this vol., p. 2065.

According to theory, the proportion in which olefin is produced in the unimolecular reaction depends on the relative rates of the final stages of the competing substitution and elimination. These final stages are immeasurably rapid, and the temperature coefficients of their rates are unknown; but any difference between the two temperature coefficients will be shown as a variation with temperature of the proportion in which olefin is formed. In the unimolecular reactions of both alkyl halides and alkylsulphonium ions the olefin proportion is, in fact, distinctly temperature-dependent, as is shown in Table IV.

TABLE IV.

Variation with temperature of the proportions in which olefins are formed in unimolecular nucleophilic substitution and elimination in ethyl alcoholic solvents (S_N1 *and* $E1$).

Solvolysis.	Solvent.	Temp.	% Olefin.	Solvolysis.	Solvent.	Temp.	% Olefin.
Bu^tCl	"80% EtOH"	25°	16·8[a]	Bu^tBr	"100% EtOH"	25°	19·0[c]
,,	,,	50	23·7	$\overset{+}{S}Me_2Am^t$,,	,,	55	27·9[d]
,,	,,	65	36·3		"80% EtOH"	50	47·8
Am^tCl	,,	25	33·0[b]	,,	,,	65	49·4
,,	,,	50	40·3[b]	,,	,,	83	53·7

(*a*) Cooper, Hughes, and Ingold, *J.*, 1937, 1280.
(*b*) Hughes and MacNulty, *J.*, 1937, 1283.
(*c*) Dhar, Hughes, and Ingold, Part XI, this vol., p. 2065.
(*d*) Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 899.

The data of Tables III and IV furnish the following picture of temperature effects on the unimolecular reactions. First, the temperature coefficients of the total first-order reactions

which alkyl chlorides, bromides, and iodides undergo in hydroxylic solvents are rather closely grouped, and, in the investigated cases, correspond to Arrhenius activation energies falling within the range 22—25 kilocals./g.-mol. Next, the temperature coefficients of the total first-order reactions of alkylsulphonium ions in hydroxylic solvents are also closely grouped in the examined examples; but the values are strikingly larger, and lead to Arrhenius energies of activation contained in the range 31—33 kilocals./g.-mol. These results, according to theory, apply to the first, slow stage of the unimolecular mechanism, *i.e.*, the heterolysis of the alkyl halide or alkylsulphonium ion. Finally, the proportion in which the total unimolecular reaction produces olefin always increases with rise of temperature. It is not remarkable that alkyl halides and sulphonium ions should be alike in this respect, since, according to theory, the effect arises from a difference in the energies of activation of the final, rapid stages of the simultaneous reactions of substitution and elimination, and these are both reactions of the separated carbonium ion. Interpreted in this way, the experimental results mean that the transference of a proton from the carbonium ion to the solvent with the formation of an olefin has an Arrhenius activation energy which is higher by about 2—4 kilocals./g.-mol. than that of the combination of the same carbonium ion with an anion extracted from the solvent. This follows if we apply the Arrhenius equation in parallel to the two rapid stages of each unimolecular reaction, taking the ratio of the amounts of the products as giving the ratio of the rates of the rapid stages, and using the data for different temperatures in order to eliminate the ratio of the frequency factors of the Arrhenius expression, and thus to isolate the difference of the activation energies.

(2) *Discussion.*—While we have as yet no completely satisfactory theory of these effects of temperature, it may be noted that the more general of the differences to which attention has been called are in the direction in which they would be if solvation were the dominant cause, and if the apparent (Arrhenius) energy of activation were a good index of the real activation energy, *i.e.*, if the two varied in a parallel manner from case to case.

Thus, for the two bimolecular reactions, S_N2 and $E2$, of alkyl halides, the initial state is the same, whereas, of the two transition states, that corresponding to elimination is the less solvated because of its more widely distributed unit charge. This is equally true for the bimolecular reactions of the alkylsulphonium ions (cf. Table I of Part VII). Solvation would therefore operate in both cases to produce a greater activation energy for elimination than for substitution; and if this difference reappears in the apparent activation energies, as derived from the Arrhenius equation, then the elimination process would have the larger temperature coefficient, and an increase of temperature would increase the proportion of olefin, as is found experimentally.

A similar statement applies to the unimolecular reactions of both alkyl halides and sulphonium salts. Here the variation with temperature of the proportion of olefin is dependent on the relative temperature coefficients of the fast stages of the competing substitution and elimination, *i.e.*, the alternative reactions of the carbonium ion. In these reactions also, a unit charge, which is localised at the commencement of the reaction-stage, becomes distributed in the transition states, but more extensively in that of the process leading to elimination (cf. Table II of Part VII). Solvation would therefore reduce the energy of the transition state of the fast stage of the elimination less than it would reduce that of the fast stage of the substitution, that is, it would contribute more largely to the energy of activatian of the former reaction than to that of the latter; and if this difference were reflected in the Arrhenius activation energies, we should find that the proportion of olefin formed in unimolecular reactions increases with temperature, as in fact it does.

We may next consider the differences between the temperature coefficients of the bi- and uni-molecular reactions of alkyl halides on the one hand, and the temperature coefficients of the analogous reactions of alkylsulphonium ions on the other. From a theoretical point of view, the principal differences, due to solvation, between corresponding reactions of the two types of alkyl compound are probably those which relate to the initial states of the reactions; for in the initial state any ionic charges which are present are localised, and therefore have their maximum effectiveness in producing solvation. In the initial state of a bimolecular reaction of an alkyl halide, one of the reactants is electrically charged and the other is neutral; whereas in the initial state of a bimolecular reaction of a sulphonium ion both reactants are charged. In the initial state of a unimolecular reaction of an alkyl halide the single reactant involved in the rate-determining process is neutral, whereas in the corresponding reaction of a sulphonium salt the single reactant is charged. Now the solvation of a charged initial state must be a powerful factor tending to increase activation energy; and it may be the main factor determining the larger apparent activation energies of the bimolecular eliminations of sulphonium salts than of

the bimolecular eliminations of the alkyl halides, as well as the considerably larger apparent activation energies of the overall unimolecular reactions of sulphonium salts than of the unimolecular reactions of the corresponding alkyl halides. We make this suggestion whilst realising that, where different types of link have to be broken, differences of activation energy are in any case to be expected, because we know of unimolecular reactions in which the bond broken is still the carbon–halogen bond, but the apparent activation energy is nevertheless increased to 29—33 kilocals./g.-mol., instead of retaining its usual value for secondary and tertiary alkyl halides of 22—25 kilocals./g.-mol.; and in these cases the special structural feature is, once again, that the sole reactant in the rate-determining stage is an ion. We are referring now to the unimolecular hydrolysis of the α-bromomethylmalonate ion and of several similar ions (Hughes and Taher, *J.*, 1940, 956; Gripenberg, Hughes, and Ingold, *Nature*, 1948, **161**, 480).

These considerations concerning the Arrhenius energies of activation require a slight extension in order to take account of the further fact that all the reactions, bimolecular and unimolecular, of the sulphonium salts have abnormally large *B*-factors. For the bimolecular reactions of sulphonium salts, the Arrhenius parameter B_2 is greater by several powers of ten than the theoretical collision frequency ($\log_{10}B_2$ is about 15, instead of the normal value of about 11, as observed, *e.g.*, in the corresponding reactions of the analogous alkyl halides). And for the unimolecular reactions of sulphonium salts, the frequency factor B_1 is of an altogether larger order of magnitude than molecular vibration frequencies ($\log_{10}B_1$ is about 17, instead of the common value of about 13, as illustrated, *e.g.*, in the corresponding reactions of alkyl halides). The unimolecular reactions of the bromomalonate ion and other bromo-anions give similarly large *B*-factors ($\log_{10}B_1$ is again about 17).

Following Gripenberg, Hughes, and Ingold (*loc. cit.*) we regard these high *B* factors as due essentially to the ionic charges in the reactants (cf. Bell, *J.*, 1943, 629); and we believe the mode of dependence to be closely connected with the effect of the charges on the activation energies. In brief, our theory is that, relatively to co-ordinate axes fixed in the reactant molecules, certain solvent molecules are restricted by these charges to positions in the initial state which are geometrically close to the positions which solvating solvent molecules will be required to occupy in the transition state of the reaction. The result will be that their displacement from one set of positions to the other will not be accompanied by as large a decrease of entropy as would have been involved in the absence of the initial charges. The small distances through which the solvating solvent molecules would have to move will, however, be associated with large amounts of electrostatic work, because of the great strength of the forces in the immediate neighbourhood of an ion. Thus the change from the initial state to the transition state will require larger increases of energy than would have been needed in the absence of the initial charges. We shall not go further into these matters here, since the structural and environmental factors which affect the Arrhenius parameters of reactions in solution are being treated in a more general manner in another paper.

Experimental.

The methods used for the preparation of materials, for following the kinetics of hydrolysis and alcoholysis of the alkyl halides and sulphonium salts, and for estimating the proportion of olefin formed, were as described in Part VI. The main numerical results are included in the preceding Tables. Details of some of the experiments are given in Tables V and VI. Other experiments are described in the accompanying papers, Parts VI, VII, XII, and XIII.

Table V.

Illustrating determinations of rates of bimolecular reactions of, and proportions of olefin formed from, alkylsulphonium ethoxide in dry ethyl alcohol.

(*a*) *Dimethyl*-tert.-*butylsulphonium Ethoxide* (*Total Rate : Expt. A*).—Solvent : EtOH. Temp. 19·98°. Initially [SMe_2Bu^tI] = 0·0200M and [NaOEt] = 0·0967N. Alkalinity, *y*, at time *t* expressed in c.c. of 0·01609N-acid per 5 c.c. sample. Rate-constant, k_2, in sec.$^{-1}$ g.-mol.$^{-1}$ l.

t (min.)	0	15	24	34	44	60	75
y (c.c.)	29·94	29·11	29·07	28·78	28·45	28·06	27·64
10^3k_2	—	(1·7)	1·10	1·07	1·11	1·08	1·12
t (min.)	117	140	160	180	200	240	∞
y (c.c.)	26·84	26·40	26·11	25·78	25·60	25·24	23·76
10^3k_2	1·09	1·12	1·13	1·17	1·15	1·14	—

(Mean 10^3k_2 = 1·12. Corrected for expansion of solvent, 10^3k_2 = 1·14.)

TABLE V (*continued*).

(*b*) *Dimethyl*-tert.-*butylsulphonium Ethoxide* (*Olefin Proportion: Expt. B.*)—Solvent: EtOH. Temp. 45·08°. Initially [SMe_2Bu^tI] = 0·0199M and [NaOEt] = 0·0958N. The alkali is expressed in c.c. of 0·01920N-acid per 5 c.c. sample, and the olefin is given by the amount of bromine, measured in c.c. of 0·02062N-thiosulphate, which survives out of a standard quantity added, in a 5 c.c. sample.

Initial readings.		Final readings.	
Alkali.	Bromine.	Alkali.	Bromine.
24·84	22·52	19·67	13·24, 12·98, 12·91, 12·75

(Olefin proportion: 97·2, 99·7, 100·6, 102·2%. Mean: 99·4%.)

Summary for ($\overset{+}{S}Me_2Bu^t$)($\bar{O}Et$). In dry ethyl alcohol k_1 at 19·98° = 114 × 10^{-5}, and k_2 at 45·08° = 2930 × 10^{-5} sec.$^{-1}$ g.-mol.$^{-1}$ l. The following proportions of *iso*butylene at 45·08° are found: 100·5%, 99·4% (Mean proportion, 100%). Hence $k(E2)$ at 19·98° = 114 × 10^{-5}, and $k(E2)$ at 45·08° = 2930 × 10^{-5} sec.$^{-1}$ g.-mol.$^{-1}$ l.; and hence for the bimolecular elimination $B = 8·5 \times 10^{14}$ sec.$^{-1}$ g.-mol.$^{-1}$ l. and $E = 24·0$ kilocals./g.-mol.

TABLE VI.

Illustrating determinations of rates of unimolecular reactions of, and proportions of olefin formed from, alkylsulphonium salts and alkyl halides in water and aqueous alcohol.

(*a*) *Dimethyl*-tert.-*butylsulphonium Salt.*—Solvent: water. Temp. 65·35°. [SMe_2Bu^tCl] initially 0·0593M. Solution initially neutral. Acidity, y, at time t, recorded in c.c. of 0·0592N-alkali for 10 c.c. sample.

t (hrs.) (uncorr.)	0·0	0·45	1·00	1·52	2·00	2·95
y (uncorr.)	0·10	0·98	1·93	2·70	3·50	4·60
10^5k_1 (k_1 in sec.$^{-1}$)	—	5·72	5·66	5·55	5·83	5·69
t (hrs.) (uncorr.)	3·75	4·80	5·80	6·80	7·80	11·50
y (uncorr.)	5·38	6·30	6·90	7·68	8·01	9·00
10^5k_1 (k_1 in sec.$^{-1}$)	5·64	5·66	5·53	5·72	5·69	—

Summary for $\overset{+}{S}Me_2Bu^tCl$. In water, k_1 at 65·35° = 5·67 × 10^{-5}, at 80·1° = 43·9 × 10^{-5}, and at 100·0° = 560 × 10^{-5} sec.$^{-1}$ (cf. Hughes and Ingold, *J.*, 1933, 1571). Hence $B_1 = 1·22 \times 10^{17}$ sec.$^{-1}$, and $E = 33·0$ kilocals./g.-mol. In "80% EtOH", k_1 at 65·35° = 11·8 × 10^{-5}, and at 80·1° = 89·7 × 10^{-5} sec.$^{-1}$. Hence $B_1 = 1·60 \times 10^{17}$ sec.$^{-1}$, and $E = 32·7$ kilocals./g. mol.

(*b*) tert.-*Butyl Chloride.*—Solvent: "80% EtOH". Temp. = 50·0°. [Bu^tCl] initially 0·182M. Solution initially neutral. Acidity, y, at time t, recorded in c.c. of 0·0510N-alkali per 10 c.c. sample. Olefin, x, recorded in c.c. of 0·0493N-thiosulphate per 20 c.c. sample.

t (hrs.) (uncorr.)	0·00	0·32	1·02	2·00	5·20	22·0	72·4
y (uncorr.)	0·33	6·70	19·58	27·70	34·62	—	35·20
x (uncorr.)	0·30	7·32	19·26	27·46	31·80	19·52	6·51

The figures show that olefin hydration becomes considerable after 2 hours. The readings up to that time give figures which are included in the summary.

Summary for Bu^tCl. In "80% EtOH", k_1 at 25·0° = 0·854 × 10^{-5}, at 50·0° = 19·6 × 10^{-5}, and at 65·35° = 89·7 × 10^{-5} sec.$^{-1}$ (cf. Cooper, Hughes, and Ingold, *loc. cit.*). Hence $B_1 = 9·8 \times 10^{11}$ sec.$^{-1}$, and $E = 23·2$ kilocals./g.-mol. The proportions of olefin at the above temperatures are given in Table IV.

(*c*) tert.-*Amyldimethylsulphonium Salt.*—Solvent: "80% EtOH". Temp. 82·7°. [SMe_2Am^tCl] initially 0·0199M. Solution initially neutral. Acidity, y, at time t, expressed in c.c. of 0·0221N-alkali per 20 c.c. sample.

t (min.) (corr.)	1·0	2·0	3·0	4·0	6·0	30·0
y (corr.)	5·09	10·05	12·09	13·83	16·07	18·00
10^5k_1 (k_1 in sec.$^{-1}$)	554	671	618	608	619	—

Mean $k_1 = 612 \times 10^{-5}$ sec.$^{-1}$. There is no appreciable hydration of olefin in the first 6 mins., and independent determinations of the olefin proportion at 4—6 mins. gave 53·7%.

Summary for SMe_2Am^tCl. In "80% EtOH", k_1 for 50·0° = 6·66 × 10^{-5}, at 65·3° = 61·8 × 10^{-5}, and at 82·7° = 612 × 10^{-5} sec.$^{-1}$. Hence $B_1 = 1·50 \times 10^{17}$ sec.$^{-1}$, and $E = 31·6$ kilocals./g.-mol. The proportions of olefin at the above temperatures are in Table IV.

SIR WILLIAM RAMSAY and RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Received, January 15th*, 1948.]

419. *Mechanism of Elimination Reactions. Part IX. Kinetics of Olefin Elimination from* n-*Propyl,* n-*Butyl,* n-*Amyl, and* iso*Butyl Bromides in Alkaline Alcoholic Media.*

By M. L. Dhar, E. D. Hughes, C. K. Ingold, and S. Masterman.

Data are recorded illustrating certain constitutional effects on the rates of the constituent substitutions and eliminations which primary alkyl bromides undergo in bimolecular reactions with ethoxide ions in ethyl alcohol. The constitutional effects studied are the lengthening of a normal chain, the successive introduction of β-linked methyl substituents, and the effect of a β-phenyl substituent.

As regards bimolecular elimination rates, the effect of increasing the normal chain-length from ethyl to *n*-propyl is to produce a marked acceleration, whilst further increase of chain-length is accompanied by a gradual decrease in the elimination rate. Successive β-linked methyl substituents continue to increase the bimolecular elimination rate, and a β-phenyl substituent increases it greatly. The significance of these results is considered in Part XVI. The changes in the bimolecular substitution rate are by no means parallel. They are in accord with a previous discussion (Dostrovsky, Hughes, and Ingold) of aliphatic substitution in terms of polar and steric influences.

This paper and those which follow are concerned with the study of constitutional effects on elimination reactions. We shall deal in this and the next two papers with olefin elimination from alkyl halides, and after that take up the case of olefin formation from sulphonium salts.

Our attack upon the constitutional problem concerning olefin formation from alkyl halides was actually commenced in Part V (Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 899). It was there pointed out that such a study cannot be conducted except in association with a kinetic analysis, the lack of which renders the extensive previous literature on olefin elimination practically useless for the purpose in view. The need arises partly from the fact that nucleophilic substitutions and eliminations commonly occur together, and have usually been measured together without discrimination. It also arises from the circumstance that substitution and elimination may each occur by either or both of two mechanisms, so that, without kinetic control, a comparison between two substances may be rendered meaningless because different mechanisms, or different mixtures of mechanisms, are, or might be, in operation in the cases compared.

In general, then, we have four component reactions, which are in principle distinguishable by a combined study of the kinetics and products of the overall reaction. The component reactions are those which we label S_N2, S_N1, $E2$, and $E1$. Our programme is to ascertain the rates of these constituent processes, or of as many of them as have measurable rates under the conditions chosen, for the reactions of a series of alkyl compounds so selected as to display the effects of progressive changes in the structure of the alkyl group.

This task was begun in Part V, which records the results of a comparative study of the reactions of ethyl, *iso*propyl, and *tert.*-butyl bromides, as well as of 2-phenylethyl and 1-phenylethyl bromides, with sodium ethoxide in dry ethyl alcohol. We have now similarly investigated a series of primary alkyl bromides, of which ethyl bromide may be regarded as the parent. The examples have been chosen in order to illustrate three types of progressive structural change, as follows. (Series 1) The series ethyl, *n*-propyl, *n*-butyl, *n*-amyl exemplifies the effects due to the progressive lengthening of a chain. (Series 2) The series ethyl, *n*-propyl, *iso*butyl illustrates the effect of successively introduced β-linked methyl substituents, and includes all the primary groups of the series from which olefins can be formed without rearrangement (the *neo*pentyl group gives olefin with rearrangement). (Series 3) The series ethyl, *n*-propyl, 2-phenylethyl is of interest in connexion with the relative magnitude of effects attributable to any hyperconjugation or conjugation of the terminal part of the radical, H, Me, Ph.

The reactions of all these compounds were conducted in ethyl-alcoholic sodium ethoxide. The common temperature was 55·0°, the same as in Part V. The initial concentration of sodium ethoxide was always about 0·1N, the alkyl halide being in deficit, so that the solutions remained alkaline. The total salt concentration was thus uniformly about 0·1M. Under these conditions kinetic complications are at a minimum, since the first-order reactions, S_N1 and $E1$, do not arise in any of the examples treated. We find in each case two second-order reactions S_N2 and $E2$, which maintain a constant ratio to each other. Our procedure is therefore to measure the rate-constant k_2 of the total second-order reaction ($S_N2 + E2$), and then split it into its components, $k(S_N2)$ and $k(E2)$, on the basis of a measurement of the proportion in which olefin is produced. Because under the alkaline conditions, olefin, when once formed,

does not enter into reaction with the solvent, such a measurement can suitably and conveniently be made towards the end of reaction.

TABLE I.

Second-order rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*), *and percentages of olefin formed, in the reactions of primary alkyl bromides with sodium ethoxide in anhydrous ethyl alcohol at* 55·0° (*concentrations* ~0·1M).

Alkyl bromide.	10^5k_2.		% Olefin.	
	Individual values.	Mean.	Individual values.	Mean.
n-Propyl	59·9, 60·1	60·0	8·7, 9·0	8·9
n-Butyl	43·9, 43·5, 44·3	43·9	9·3, 10·4	9·8
n-Amyl	39·6, 38·9	39·2	8·5, 9·3	8·9
*iso*Butyl	14·3, 14·3, 14·3, 14·1	14·3	58·2, 58·6, 61·0, 60·4	59·5

Table I contains the new measurements of the total bimolecular rate constants, and of the proportions in which olefin is formed, in the reactions of the alkyl bromides. In Table II these data, as well as corresponding data, taken from the record in Part V, for two other primary alkyl bromides, are analysed in terms of the rate constants of the individual bimolecular reactions of substitution and elimination, S_N2 and $E2$.

TABLE II.

Analysis of the kinetic data for the reactions of primary alkyl bromides with sodium ethoxide in ethyl alcohol at 55°, *showing the variation of the rates of bimolecular substitution and bimolecular elimination with progressive changes in the structure of the alkyl group.*

Series.	Alkyl bromide.	10^5k_2.	% Olefin.	$10^5k(S_N2)$.	$10^5k(E2)$.
1	$CH_3{\cdot}CH_2Br$	174	0·9	172	1·6
	$CH_3{\cdot}CH_2{\cdot}CH_2Br$	60·0	8·9	54·7	5·3
	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Br$	43·9	9·8	39·6	4·3
	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Br$	39·2	8·9	35·7	3·5
2	$CH_3{\cdot}CH_2Br$	174	0·9	172	1·6
	$CH_3{\cdot}CH_2{\cdot}CH_2Br$	60·0	8·9	54·7	5·3
	$(CH_3)_2CH{\cdot}CH_2Br$	14·3	59·5	5·8	8·5
3	$CH_3{\cdot}CH_2Br$	174	0·9	172	1·6
	$CH_3{\cdot}CH_2{\cdot}CH_2Br$	60·0	8·9	54·7	5·3
	$C_6H_5{\cdot}CH_2{\cdot}CH_2Br$	593	94·6	32	561

The figures in Table II are arranged in such a way as to show the variation of the different rates, and of the olefin proportions, in the three structural series which the available data allow us to illustrate. We need not now comment on the substitution rates, since the stronger variations have recently been theoretically discussed in terms of the polar and steric effects exhibited by alkyl groups in bimolecular reactions (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173). As to the elimination rates we shall here restrict ourselves to pointing out the empirical relations; which are that a progressive increase in the chain-length of the alkyl group is accompanied at first by a marked increase, and then by a gradual decrease, in the bimolecular elimination rate; that successive β-linked methyl substituents in the alkyl group considerably increase the rate; and that a β-phenyl substituent greatly increases the rate. A theoretical discussion of these relationships is included in Part XVI.

EXPERIMENTAL.

Materials.—Commercial *n*-propyl, *n*-butyl, and *n*-amyl bromides were dried with anhydrous potassium carbonate and with calcium chloride and fractionated. The fractions having the respective b. p.s 70·8°/755 mm., 101·5°/767 mm., and 127·7°/754 mm. were taken for the measurements now reported. The available sample of *iso*butyl bromide was found to contain *tert.*-butyl bromide as an impurity. This was destroyed by shaking the material for 3 hours at 20° with dilute aqueous sodium hydroxide containing acetone. After addition of excess of water, the unchanged bromide was recovered, dried, and fractionated. It had b. p. 91·5°/760 mm. The alcohol used as solvent was prepared by drying commercial absolute alcohol by the method of Lund and Bjerrum (*Ber.*, 1931, **64**, 210).

Method of Kinetic Measurements.—Portions, usually 5·0 c.c., of the reaction mixture, taken from a standard measuring flask, were enclosed in the cold in sealed tubes, which were placed in the thermostat (55·0° ± 0·05°) for known times, and then broken each under 100 c.c. of cold anhydrous ethyl alcohol

in order to stop the reaction. The surviving alkali was then titrated with standard hydrochloric acid, with the use of lacmoid as indicator. Second-order rate constants were calculated from the formula $k_2 = \{1/t(a-b)\}\log_e\{b(a-x)/a(b-x)\}$, where t is the time in seconds, a and b are the initial concentrations of alkali and alkyl bromide, and x is the concentration of alkali destroyed in time t. The constants thus obtained were corrected for the change in volume of the solvent between the temperature at which the solutions were made up and the temperature of the thermostat.

Methods for Olefin Estimations.—Propylene was estimated by the aspiration method (Hughes, Ingold, and Shapiro, *J.*, 1936, 230), and all other olefins by the extraction method (Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 901). Experiments by the latter method were always conducted in the following way. About 14 samples of the original solution in sealed bulbs were simultaneously placed in the thermostat, and about half of them were removed and chilled after two minutes, this moment being regarded as the time of commencement of the reaction to be investigated. Two of the removed tubes were used for the estimation of free alkali as described above, and the others were employed for the estimation of any olefin which might have been formed during the period in which the temperature was being raised to that of the thermostat. The other tubes were removed from the thermostat and chilled after a time sufficient to allow the decomposition to proceed nearly to completion. Again two tubes were used to estimate surviving alkali, and the others in order to estimate the olefin present. The amount of total reaction, and the amount of olefin formed, between the two times, could then be deduced, and hence the production of olefin could be calculated as a fraction of the total reaction.

Results of Measurements.—These are summarised in Table I. As illustrations, an individual measurement of the total bimolecular rate-constant, k_2, for *n*-butyl bromide is recorded in Table III, and an individual measurement of the proportion in which butylene is produced from *n*-butyl bromide is given in Table IV.

TABLE III.

Illustrating determinations of total second-order rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*) : n-*butyl bromide* (*Expt. C*).

(Solvent : EtOH. Temp. : 55·0°. Initially [BuBr] = 0·08762M and [NaOEt] = 0·1038N. In the Table, [BuBr] and [NaOEt] are each expressed in c.c. of 0·03107N-acid per 5 c.c. sample.)

t (min.).	[NaOEt].	[BuBr].	10^4k_2.	t (min.).	[NaOEt].	[BuBr].	10^4k_2.
0	16·70	14·10	—	508	8·46	5·86	4·01
25	15·81	13·21	4·36	560	8·05	5·45	4·06
60	14·70	12·10	4·35	767	6·92	4·32	4·07
97	13·73	11·13	4·35	895	6·30	3·70	4·17
125	13·05	10·45	4·24	1110	5·60	3·00	4·22
180	11·94	9·34	4·42	1243	5·35	2·75	4·11
235	11·10	8·50	4·28	1328	5·20	2·60	4·06
295	10·33	7·73	4·20	1387	5·08	2·48	4·06
355	9·55	6·95	4·31	1958	4·22	1·62	4·14
445	8·83	6·23	4·16	" ∞ "	2·60	0·00	—

(Mean k_2, 4·19 × 10^{-4}; corrected for solvent expansion, 4·43 × 10^{-4} sec.$^{-1}$ g.-mol.$^{-1}$ l.)

TABLE IV.

Illustrating determinations of olefin proportions by the extraction method : n-*butyl bromide* (*Expt. B*).

(Solvent : EtOH. Temp. : 55·0°. Initially [BuBr] = 0·08139M and [NaOEt] = 0·1008N. Portions of 20 c.c. were used for estimation of alkali and olefin. In the Table the alkali in each sample is expressed in c.c. of 0·06244N-acid, whilst the olefin is given by the amount of bromine, measured in c.c. of 0·1972N-thiosulphate, which survives out of 5·0 c.c. of added standard bromine.)

Initial readings.		Final readings.	
Alkali.	Bromine.	Alkali.	Bromine.
32·32	20·80, 20·65, 20·77	6·22	19·05, 18·80, 19·15
32·25	20·68, 20·68	6·20	19·27, 18·90, 18·84
32·28 (mean)	20·72 (mean)	6·21 (mean)	19·00 (mean)

(Alkali consumed : 24·07 c.c. Olefin formed : 1·72 c.c. Olefin = 10·4%.)

Products.—Since *iso*butyl bromide is known to undergo transformation to *tert.*-butyl bromide at elevated temperatures, it was considered desirable to show that no such change could have occurred under the conditions of the alkaline alcoholysis to which the kinetic measurements apply. *iso*Butyl bromide was therefore boiled for 40 hours with dilute sodium hydroxide, and the alcohol thereby formed was isolated. It was identified as *iso*butyl alcohol by conversion into the *p*-nitrobenzoate, m. p. 70—71°, and a determination of the mixed melting point of the latter with an authentic specimen.

In order to confirm the individuality of the *iso*butylene produced by the hydrolysis of *iso*butyl bromide, the olefin, generated from 50 g. of *iso*butyl bromide and 500 c.c. of 2N-ethyl-alcoholic sodium ethoxide, was led through a series of condensers and traps designed to retain alcohol, and was collected at −80° and distilled. It was then carefully combined with bromine in methylene chloride solution. The dibromide on distillation showed the characteristics of an almost pure substance, and had the b. p., 60—61°/35 mm., and refractive index $n_D^{20°}$ 1·5102, of the dibromide of *iso*butylene.

SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Received, January 15th,* 1948.]

420. *Mechanism of Elimination Reactions. Part X. Kinetics of Olefin Elimination from* iso*Propyl,* sec.*-Butyl,* 2-n-*Amyl, and* 3-n-*Amyl Bromides in Acidic and Alkaline Alcoholic Media.*

By M. L. Dhar, E. D. Hughes, and C. K. Ingold.

Data are recorded to show certain constitutional effects on the rates of the constituent substitutions and eliminations which secondary alkyl bromides undergo in bimolecular reactions with ethoxide ions in anhydrous ethyl alcohol, and also in solvolytic reactions with 60% aqueous ethyl alcohol. Elimination rates are analysed, where possible, into those of the component elimination processes which establish the double bond in alternative branches of the secondary alkyl group. The structural effects studied relate to increases in alkyl chain-length beyond the β-carbon atom in either or both of the branches of the secondary group.

The bimolecular substitution rate drops with ascent of a homologous secondary alkyl series more slowly than it drops in an analogous primary alkyl series; and it drops somewhat more slowly in the secondary series when less concentrated alkali is employed for the reaction. These quantitative differences are ascribed to the operation of mixed mechanisms near the conditions for change to the unimolecular mechanism of substitution. Bimolecular elimination rate is increased by the introduction of β-linked methyl substituents in either or both of the alkyl branches, and is decreased, but less sharply, if such a branch is further lengthened by continued alkyl substitution. Each change of elimination rate from one compound to another is more than accounted for by a change in the rate of establishment of the double bond in the altered alkyl branch, this effect being partly off-set by smaller contrary changes in the rate of entrance of the double bond into the alkyl branches which remain similar. These relations are interpreted in Part XVI.

The solvolytic reactions in neutral and acidic aqueous alcohol consist in part of bimolecular substitution with a solvent molecule as substituting agent, and in part of unimolecular substitution and elimination. Because of the composite molecularity of the total solvolytic substitution, no attempt is made to analyse the obviously complicated structural effects on the solvolytic substitution rate. However, the solvolytic elimination will be wholly unimolecular in mechanism, and its rate should be intelligibly related to structure. It is found that the unimolecular elimination rate is increased by the introduction of a β-linked methyl substituent in either or both of the alkyl branches, and is decreased, but less sharply, if such a branch is further lengthened by continued alkyl substitution. These effects also are interpreted in Part XVI.

The investigation of constitutional effects on olefin elimination from secondary alkyl halides provides a more complicated problem than did the similar study of primary halides described in the preceding paper. For this there are several reasons.

One is that in secondary alkyl halides the tendency towards bimolecular and unimolecular reactions of substitution and elimination are all developed to an appreciable extent. Therefore, in general, at least four reactions, those to which we give the type-labels S_N2, $E2$, S_N1, and $E1$, require to be kinetically separated, and individually studied with respect to constitutional influences.

Of these four processes, the two bimolecular reactions, S_N2 and $E2$, can readily be examined, without serious interference from the unimolecular reactions, by the use of a somewhat weakly ionising solvent, such as anhydrous ethyl alcohol, and moderately large concentrations of strongly basic reagents, such as hydroxide or ethoxide ion. On the other hand, even in alcohol–water mixtures of marked ionising character, the tendency shown by secondary alkyl halides to undergo the unimolecular reactions S_N1 and $E1$ is not usually so great that these processes can be kinetically isolated from the bimolecular reactions in the presence of conveniently measurable concentrations of alkali. One is therefore compelled to pursue the kinetic study of the unimolecular reactions in nearly neutral and acidic solutions, thereby introducing the well-known difficulty, peculiar to solvolytic processes, of distinguishing between true unimolecular reactions involving the prior ionisation of the alkyl halide, and bimolecular reactions in which the solvent molecule is the reagent. These two types of reaction may both exhibit accurate or approximate first-order kinetics, and therefore the distinction between them usually has to depend on indirect evidence of various kinds.

The remaining general point concerning secondary alkyl halides is that some of them are so constituted that different olefins can be formed from them by elimination along different branches of the alkyl structure. It follows that the set of simultaneous reactions requiring separate measurement in a given case, and comparison from case to case, may include two concurrent eliminations of either kinetic type.

The following alkyl halides have been included in the present study: *iso*propyl, *sec.*-butyl, 2-*n*-amyl, and 3-*n*-amyl bromide. The first and fourth of these can each give rise to only one

olefin, whilst the second and third can, and do, each produce a mixture of two isomeric olefins (three, allowing for the geometrically isomeric forms of one of the position isomerides). The examples are chosen in order to provide two series, one of which illustrates the effects of progressive homology through the lengthening of a chain, whilst the other exemplifies the effect of the introduction of successive β-linked methyl groups: Series 1: $CH_3(CHMeBr)$, $CH_3{\cdot}CH_2(CHMeBr)$, $CH_3{\cdot}CH_2{\cdot}CH_2(CHMeBr)$. Series 2: $Me_2(CHBr)$, $MeEt(CHBr)$, $Et_2(CHBr)$.

There are several relevant previous investigations. The set of simultaneous substitutions and eliminations undergone by *iso*propyl bromide under various conditions of alkalinity were kinetically analysed by Hughes, Ingold, and Shapiro (*J.*, 1936, 225). They employed two solvents, " 60% " aqueous ethyl alcohol (a mixture of 3 vols. of ethyl alcohol and 2 vols. of water) and " 80% " ethyl alcohol (4 vols. of alcohol plus 1 vol. of water), and a range of temperatures. Hughes, Ingold, Masterman, and MacNulty (*J.*, 1940, 899) extended the work, employing anhydrous ethyl alcohol as solvent, and a wide range of ionic strengths, but only one temperature, this being chosen for its suitability in the comparison of typical primary, secondary, and tertiary alkyl halides having very different kinds of reactivity. An investigation of olefin elimination from 2-*n*-butyl and 2-*n*-amyl bromide has been carried out by Lucas and his collaborators (Lucas, Simpson, and Carter, *J. Amer. Chem. Soc.*, 1925, **47**, 1462; Lucas, Dillon, and Young, *ibid.*, 1930, **52**, 1949). Without making any kinetic measurements on the processes studied, these authors carried out some careful determinations of the compositions of the mixtures of isomeric olefins which are formed from each halide by the action of hot ethyl-alcoholic potassium hydroxide.

In the present work, anhydrous ethyl alcohol has been used for the investigation of the bimolecular processes, and " 60% " aqueous ethyl alcohol for that of the unimolecular reactions. The bimolecular reactions in dry ethyl alcohol have been studied under two sets of conditions. In the first, the reagent was 4N-potassium hydroxide, and the temperature 80·0°, these conditions being chosen in order that the kinetic results could be correlated with the above-mentioned analytical work of Lucas and his collaborators. However, although the reaction rates could be measured in these conditions, the reactions were rather too fast for accurate kinetic study by our methods. Furthermore, the reagent is not as simple as it could be, since the entity which attacks the alkyl halide molecules, though it probably consists mainly of ethoxide ions, must actually be a mixture of hydroxide and ethoxide ions. We have therefore endeavoured to secure a series of more accurate, and possibly more simply interpretable, kinetic data by means of a parallel series of measurements under a second set of conditions, in which the reagent was 1N-sodium ethoxide and the temperature 25·0°, the solvent being dry ethyl alcohol as before.

It can be shown that, in the presence of 4N-potassium hydroxide in dry ethyl alcohol at 80°, the total reaction is substantially bimolecular: the incursion of first-order processes amounts to less than 1%, and is therefore negligible. We are thus dealing essentially with the substitution and elimination processes S_N2 and $E2$. Just as in the corresponding study with primary halides (Part IX), two types of measurement were made in each example. First, we measured the total bimolecular rate constant, k_2, by following the liberation of halide ion. Then we determined the proportion in which the total reaction yields olefin, and on that basis split up the over-all constant, k_2, into its component parts, $k(S_N2)$ and $k(E2)$, relating to the substitution and elimination. Since the solutions are alkaline, olefin, when once formed, is not destroyed, and hence the proportion in which it is produced can conveniently be estimated at the conclusion of reaction.

In those cases in which the elimination constant, $k(E2)$, is itself composite, owing to the simultaneous formation of isomeric olefins, this constant can be split into its components with the help of Lucas's analytical data. These are given in the following scheme, if one reads the upper line of figures entered against the butylenes. Lucas's analysis of the mixture of butylenes has been repeated by Dr. L. I. Woolf, as described in Part XIII. His results are summarised in the lower line of figures given for the butylenes. We use the mean of Lucas's and Woolf's results in our analyses of the elimination rate-constants, $k(E2)$:

$$CH_3{\cdot}CH_2{\cdot}CH(CH_3)Br \xrightarrow[(E2)]{\bar{O}Et} CH_3{\cdot}CH{=}CH_2\ (82{\cdot}5\%\ /\ 80{\cdot}0\%) + CH_3{\cdot}CH_2{\cdot}CH{=}CH_2\ (17{\cdot}5\%\ /\ 20{\cdot}0\%)$$

$$CH_3{\cdot}CH_2{\cdot}CH(CH_3)Br \xrightarrow[(E2)]{\bar{O}Et} CH_3{\cdot}CH_2{\cdot}CH{=}CH(CH_3)\ (71{\cdot}0\%) + CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH{=}CH_2\ (29{\cdot}0\%)$$

Lucas and his co-workers were unable to determine the proportion in which the but-2-ene

is composed of *cis*- and *trans*-isomerides. According to Woolf, the but-2-ene consists almost entirely of the *cis*-compound.

In the presence of 1N-sodium ethoxide in anhydrous ethyl alcohol at 25°, the total reaction is still substantially bimolecular although the incursion of first-order processes may amount to 2 or even 3%. We still treat the reaction as containing essentially only the processes S_N2 and $E2$, and, as before, determine the total bimolecular rate-constant, and the olefin proportion, in each example. We have analysed the results as before, even to the stage in which Lucas's and Woolf's results are employed, since the kinetic constants are certainly more accurate, and we think that Lucas's and Woolf's olefin compositions will apply under the changed conditions to quite a good approximation, perhaps to within the limits of the errors in the measurements themselves (cf. Part XIV).

Table I contains the observational data for both the sets of conditions specified. In Table II these data are analysed in the manner described. The figures are arranged to show the effects arising from the two types of progressive structural change which our compounds illustrate.

TABLE I.

Second-order rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*), *and percentages of olefin formed, in the reactions of secondary alkyl bromides with potassium hydroxide and with sodium ethoxide in anhydrous ethyl alcohol.*

Conditions.	Alkyl bromide.	10^5k_2.	% Olefin.	
			Determinations.	Mean.
4N-KOH at 80·0°	2-Propyl	162	88·0, 86·2	87·1
	2-*n*-Butyl	209	90·0, 92·8	91·4
	2-*n*-Amyl	165	91·6, 89·2	90·4
	3-*n*-Amyl	211	96·0, 97·7	96·8
1N-NaOEt at 25·0°	2-Propyl	0·295	82·7, 78·0	80·3
	2-*n*-Butyl	0·422	82·3, 79·7, 84·6	82·2
	2-*n*-Amyl	0·343	79·4, 82·0	80·7
	3-*n*-Amyl	0·454, 0·455	87·5, 88·6	88·1

We shall comment here only on the substitution rates, since the elimination rates will be comprehensively considered later and in Part XVI. Since the olefin estimations admit of possible errors up to 3% (cf. Hughes, Ingold, Masterman, and MacNulty, *loc. cit.*), the figures $10^5k(S_N2)$ given in Table II for the reactions with 4N-potassium hydroxide are liable to errors up to 5 units, whilst the corresponding figures for the reactions with 1N-sodium ethoxide involve possible errors of 0·01. In the former case it would seem that a fall of rate accompanies ascent of the homologous series, though the details are obscured by the experimental error. In the latter, all that can be said is that the values show no marked trend in either direction.

We interpret these facts, as similar phenomena have been interpreted before, by reference to our view that it would be an over-simplification to regard the transition from the bimolecular to the unimolecular mechanism of substitution as a sharp change. There must be degrees of coupling between the bond-breaking and bond-forming processes involved in a substitution, and, in conditions near to those which would change the mechanism, many molecules may react along paths which cannot clearly be classified as belonging to either mechanism. The consequence is that, as the conditions for a change of mechanism are approached, signs of the impending change, *e.g.*, particular types of variation of rate with structure or with solvent, may begin to appear before all the kinetic characteristics of the new mechanism are fully developed. One recognises that isolated small rate differences are unlikely in principle to have any simple relation to structure; and furthermore that some of the measurements of substitution rates involve a considerable experimental error. Nevertheless it is clear that the drop of rate with ascent of the homologous series is significantly less in the secondary alkyl series than in the primary alkyl series discussed in the preceding paper. It also seems fairly clear that the drop of rate with ascent of the secondary series is less with the weaker alkali than with the stronger. These tendencies accord with the ideas indicated, inasmuch as in passing from the primary to the secondary alkyl series, as well as in passing from more to less alkaline solutions, one is approaching more closely to the conditions in which the unimolecular mechanism takes control. It is possible to express the whole argument in terms of potential energy surfaces, as has been done in an analogous case (cf. Hughes, Ingold, and Shapiro, *loc. cit.*).

TABLE II.

Analysis of kinetic data for the reactions of secondary alkyl bromides with potassium hydroxide and with sodium ethoxide in ethyl alcohol, showing the variation of the rates of bimolecular substitution and bimolecular elimination with progressive changes in the structure of the alkyl group.

Conditions.	Series.	Alkyl bromide.	10^5k_2.	% Olefin.	10^5k (S_N2).	$10^5k(E2)$. Total.	Each branch.
4N-KOH in EtOH at 80·0°	1	CH_3>CHBr CH_3	162	87·1	21	141	70, 70
		$CH_3\cdot CH_2$>CHBr CH_3	209	91·4	18	191	156, 35
		$CH_3\cdot CH_2\cdot CH_2$>CHBr CH_3	166	90·4	16	150	106, 44
	2	CH_3>CHBr CH_3	162	87·1	21	141	70, 70
		$CH_3\cdot CH_2$>CHBr CH_3	209	91·4	18	191	156, 35
		$CH_3\cdot CH_2$>CHBr $CH_3\cdot CH_2$	211	96·8	7	204	102, 102
1N-NaOEt in EtOH at 25·0°	1	CH_3>CHBr CH_3	0·295	80·3	0·058	0·237	0·118, 0·118
		$CH_3\cdot CH_2$>CHBr CH_3	0·422	82·2	0·075	0·347	0·282, 0·065
		$CH_3\cdot CH_2\cdot CH_2$>CHBr CH_3	0·343	80·7	0·067	0·276	0·196, 0·080
	2	CH_3>CHBr CH_3	0·295	80·3	0·058	0·237	0·118, 0·118
		$CH_3\cdot CH_2$>CHBr CH_3	0·422	82·2	0·075	0·347	0·282, 0·065
		$CH_3\cdot CH_2$>CHBr $CH_3\cdot CH_2$	0·455	88·1	0·054	0·401	0·200, 0·200

The simultaneous substitution and elimination reactions which the same series of secondary alkyl halides undergoes at 80·0° in neutral and acidic " 60% " aqueous ethyl alcohol have also been studied. The total reaction, as measured by the development of acidity, is now of the first order. In each case, we have measured the total rate constant, k_1, and also the proportion of olefin formed in the reaction. Since the olefin in these experiments is produced in acidic solutions the precautions, described in Part VI (this vol., p. 2041), had to be taken in order to obviate error due to loss of formed olefin through the acid-catalysed addition of solvent molecules to form an alcohol or an ether. The experimental results are in Table III. The value of the rate-constant for *iso*propyl bromide, as deduced from Hughes, Ingold, and Shapiro's results (*loc. cit.*) by extrapolation with respect to temperature, is $7{\cdot}83 \times 10^{-5}$ sec.$^{-1}$, and is thus higher than that now recorded. The most probable cause of the difference is a slight difference of solvent-composition. A still higher value, $9{\cdot}08 \times 10^{-5}$ sec.$^{-1}$, was recorded by Hughes and Shapiro (*J.*, 1937, 1192); but in this case the solutions were deliberately made up in a complicated way for the purpose of a special comparison, and a difference of solvent-composition is to be expected. In the present experiments a single batch of " 60% " aqueous alcohol was drawn upon for all the rate determinations recorded in Table III.

The unimolecular substitution and elimination reactions, S_N1 and $E1$, have a common slow stage, *viz.*, the ionisation of the alkyl halide. If we knew that the whole of the observed first-

TABLE III.

First-order rate-constants (k_1 *in sec.*$^{-1}$), *and percentages of olefin formed, in the reactions of secondary alkyl bromides in neutral and acidic "* 60% *" aqueous ethyl alcohol at* 80·0°.

Alkyl bromides.	10^5k_1.		% Olefin.	
	Determinations.	Mean.	Determinations.	Mean.
2-Propyl	7·06, 7·06	7·06	4·7, 4·2, 4·9	4·6
2-*n*-Butyl	7·46, 7·37	7·41	8·7, 8·4	8·5
2-*n*-Amyl	5·61	5·61	5·8, 6·2, 5·7, 8·6	6·8
3-*n*-Amyl	5·91, 6·03	5·97	14·4, 14·3, 17·4, 14·3	15·1

order reaction were indeed unimolecular, then we should interpret the first-order rate-constant k_1, as measuring the rate of ionisation, and the proportion of olefin as giving the ratio in which the alkyl carbonium ion, produced by the ionisation, is partitioned in the final, rapid stages of substitution and elimination. However, it has been recognised since 1940 that some part of the first-order solvolytic reactions of secondary alphyl halides in aqueous alcoholic solvents consist of bimolecular substitutions in which a neutral solvent molecule is the substituting agent (Bateman, Cooper, Hughes, and Ingold, *J.*, 1940, 925; Dostrovsky, Hughes, and Ingold, *J.*, 1946, 191). The precise proportions in which these bimolecular solvolytic substitutions are present are still not exactly known, but attempts to secure definite measurements are in hand. From this situation it follows that neither the overall first-order constant, k_1, nor the proportion of olefin, can safely be concluded to have any simple and exact mechanistic significance. However, one may expect that, if the olefin proportions are used in order to analyse the total first-order rates into their constituent substitution and elimination rates, then any complications arising from the composite molecularity will become concentrated in the substitution constants, leaving the elimination constants with the significance of true unimolecular rate-constants. The reason for this expectation is that, when the basicity of a nucleophilic reagent is progressively reduced, its power of attacking hydrogen and thereby producing a bimolecular elimination disappears much more rapidly than its power of attacking carbon and thus participating in a bimolecular nucleophilic substitution (Hughes, Ingold, Masterman, and MacNulty, *loc. cit.*). Our knowledge of this phenomenon makes it appear most improbable that bimolecular eliminations involving solvent molecules as reagent could occur to any significant extent under the conditions of our measurements.

We have analysed the data of Table III on these lines, and the resulting figures are in Table IV. They are arranged to show the effects which arise from the progressive lengthening of a carbon chain, and from successively introduced β-linked methyl substituents. Our analysis is incomplete in the respect that although the olefins formed from 2-*n*-butyl and 2-*n*-amyl bromide will certainly be mixtures of isomerides, we have not analysed them owing to the difficulties created by the small yields. and have therefore been unable to split up the elimination constants, $k(E1)$, into components representing elimination along the different branches of the alkyl groups.

The substitution constants of Table IV show no marked and simple dependence on structure within the limits illustrated. This can be explained either on the grounds that the conditions are near those of mechanistic change, or by means of the theory that these constants represent rates of mixtures of substitution processes of different molecularities and largely opposing trends with respect to variation of rate with structure. On the other hand, the elimination constants have a simple and easily intelligible connexion with structure.

We shall here restrict comment on the elimination rates to pointing out the similarity in the structural variation of the bimolecular and the unimolecular elimination rates (cf. Tables II and IV). In the series *iso*propyl, *sec.*-butyl, 2-*n*-amyl, both the *E*2 and *E*1 rates increase fairly sharply from the first member to the second, and then decrease less sharply from the second to the third. In the series *iso*propyl, *sec.*-butyl, 3-*n*-amyl, both the *E*2 and *E*1 rates exhibit similar increases from the first to the second, and from the second to the third, of the homologues. The further analysis that was possible in the case of the bimolecular eliminations shows that every change of rate, no matter what its direction may be, from one compound to another is always more than accounted for by a change in the rate of establishment of the olefinic double bond in that branch of the alkyl group which has become altered, this effect being partly offset by opposite changes of smaller magnitude in the rate of entrance of the double bond into the

TABLE IV.

Analysis of kinetic data for the reactions of secondary alkyl bromides with " 60% *" aqueous alcohol at* 80·0°, *showing the variation in the first-order substitution rates and unimolecular elimination rates with progressive changes in the structure of the alkyl group.*

Series.	Alkyl bromide.	10^5k_1.	% Olefin.	10^5k (" S_N1 ").	$10^5k(E1)$.
1	CH_3>CH_3>CHBr	7·06	4·6	6·74	0·32
	$CH_3\cdot CH_2$>CH_3>CHBr	7·41	8·5	6·78	0·63
	$CH_3\cdot CH_2\cdot CH_2$>CH_3>CHBr	5·61	6·8	5·23	0·38
2	CH_3>CH_3>CHBr	7·06	4·6	6·74	0·32
	$CH_3\cdot CH_2$>CH_3>CHBr	7·41	8·5	6·78	0·63
	$CH_3\cdot CH_2$>$CH_3\cdot CH_2$>CHBr	5·97	15·1	5·07	0·90

alkyl branches which remain similar. The theoretical interpretation of these relationships will be considered in Part XVI.

EXPERIMENTAL.

Materials.—Commercial *iso*propyl bromide was dried and fractionated: it had b. p. 60°/760 mm. 2-*n*-Butyl, 2-*n*-amyl, and 3-*n*-amyl bromide were prepared by the action of hydrogen bromide on the pure synthetic alcohols. Dried and fractionated, they had b. p. 91·5°/757 mm., 118°/746 mm., and 117°/758 mm. respectively. The solvent ethyl alcohol was dried by Lund and Bjerrum's method. A large batch of " 60% " aqueous alcohol was made by mixing 3 vols. of anhydrous ethyl alcohol with 2 vols. of distilled water at 20°.

Methods for Kinetic Measurements.—Owing to the considerable concentrations of alkali present in the second-order reactions, these were followed by estimating halide ions by Volhard's method. Portions of the reaction mixture, usually 5 c.c., were enclosed in the cold in sealed tubes, which, after being heated in the thermostat, were broken each under 100 c.c. of 2·5N-nitric acid (halogen-free) and 60 c.c. of ether. The solution was shaken, and the aqueous layer, and a further aqueous extract of the ethereal layer, were run into 50 c.c. of ether and a known volume of standard silver nitrate solution. The excess of silver was then determined by titration with thiocyanate. In the experiments with sodium ethoxide, second-order rate-constants were calculated from the formula $k_2 = \{1/t(a-b)\}\log_e\{b(a-x)/a(b-x)\}$, where t is the time in seconds, a and b are the initial concentrations of sodium ethoxide and alkyl bromide, and x is the concentration of halide liberated at time t. In the experiments with concentrated potassium hydroxide, first-order constants were calculated from the formula $k_1 = (1/t)\log_e\{b/(b-x)\}$ where t, b, and x have their previous meanings; and then these constants were converted into second-order constants, k_2, by division by a, the initial concentration of the alkali. In both cases the second-order constants were corrected for the change of volume of the solvent between the temperature at which the solutions were made up and measured and the temperature of the thermostat.

The first-order reactions were also carried out in small sealed tubes, but in this case the development of acid was followed. Each tube containing a sample to be analysed was broken under 100 c.c. of acetone, and the liberated hydrogen bromide was titrated with standard alkali, with the use of lacmoid as indicator. First-order rate-constants were calculated from the formula $k_1 = (1/t)\log_e\{b(b-x)\}$, where the symbols have their previous meanings.

Method for Olefin Estimations.—The olefins were estimated by the extraction method, even propylene, although a correction of 6—8% for losses is necessary in this case (cf. Hughes, Ingold, Masterman, and MacNulty, *loc. cit.*). The estimations of olefin formed in the alkaline solutions were made as described in the preceding paper: the amounts of halide ion and olefin simultaneously present at two times, one near the beginning and one towards the conclusion of a run, were estimated, and the proportion in which the reaction results in olefin was calculated from the differences. The estimations of olefin formed in acid solution required a " pilot " experiment, in which olefin and halide ion were estimated at various times during the course of a run in order to discover the range of times during which the most accurate estimates could be made. Such times were used in subsequent estimations. The best times are those which allow as long as possible for the development of olefin, before the disappearance of olefin, through acid-catalysed solvent-addition, becomes appreciable. The corrections for losses of olefin, which are hardly appreciable except in the case of propylene, were determined by blank experiments.

Results of Measurements.—These are summarised in Tables I and III. Examples of the different types of measurement are given in Tables V—X.

TABLE V.

Illustrating determinations of first- and second-order rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*; k_1 *in sec.*$^{-1}$) *in reactions of secondary alkyl bromides with* 4N-*ethyl-alcoholic potassium hydroxide :* iso*propyl bromide.*

(Solvent : EtOH. Temp. 80·0°. Initially [Pr^{i}Br] = 0·1503M and [KOH] = 3·955N. In this Table [Pr^{i}Br] is expressed in c.c. of 0·07333N-thiocyanate per 5 c.c. sample.)

t (min.).	[Pr^{i}Br].	10^4k_1.	10^4k_2.	t (min.).	[Pr^{i}Br].	10^4k_1.	10^4k_2.
0·0	10·25	—	—	4·5	1·95	61·4	15·5
0·5	8·55	60·4	15·2	5·5	1·40	60·3	15·2
1·0	7·01	63·3	16·0	6·5	0·95	60·9	15·4
1·5	5·80	63·2	16·0	7·5	0·70	59·6	15·0
2·0	5·10	58·1	14·7	8·5	0·50	59·2	14·9
2·5	4·20	59·5	15·0	10·0	0·30	58·8	14·8
3·5	2·92	59·8	15·1	15·0	0·10	—	—

(Mean 10^4k_1 = 60·3. Mean 10^4k_2 = 15·3. Corrected for expansion 10^4k_2 = 16·2.)

TABLE VI.

Illustrating determinations of olefin proportions in reactions of secondary alkyl bromides with 4N-*ethyl-alcoholic potassium hydroxide :* iso*propyl bromide* (*Expt. A*).

(Solvent : EtOH. Temp. 80·0°. Initially [Pr^{i}Br] = 0·1582M and [KOH] = 3·955N. Portions of 10 c.c. used for estimation of bromide ion and olefin. In the Table the bromide ion is given by the silver, measured in c.c. of 0·09065N-thiocyanate, which survives out of 20 c.c. of added standard silver nitrate, and the olefin is given by the bromine, measured in c.c. of 0·1686N-thiosulphate, which remains out of 10 c.c. of added standard bromine.)

Initial readings.		Final readings.	
Silver.	Bromine.	Silver.	Bromine.
22·75	36·6, 36·3, 36·8, 36·4	5·20, 5·25	21·4, 21·0, 21·2, 21·8
22·70	36·7, 36·5, 36·6	5·31	21·6, 21·6, 20·8
22·73 (mean)	36·55 (mean)	5·27 (mean)	21·20 (mean)

(Proportion of olefin = 81·8%. Proportion corrected for losses = 88·0%.)

TABLE VII.

Illustrating determinations of second-order rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*) *in reactions of secondary alkyl bromides with* 1N-*alcoholic sodium ethoxide :* iso*propyl bromide.*

(Solvent : EtOH. Temp. 25·0°. Initially [Pr^{i}Br] = 0·2054M and [NaOEt] = 0·9783N. In the Table [Pr^{i}Br] and [NaOEt] are both expressed in c.c. of 0·09049N-thiocyanate per 5 c.c. sample.)

t (min.).	[NaOEt].	[Pr^{i}Br].	10^5k_2.	t (min.).	[NaOEt].	[Pr^{i}Br].	10^5k_2.
0	54·06	11·35	—	4955	47·81	5·10	2·94
115	53·84	11·13	2·90	5720	47·26	4·55	2·93
195	53·68	10·97	2·95	7200	46·41	3·70	2·90
395	53·31	10·60	2·96	8640	45·71	3·00	2·90
740	52·76	10·05	2·83	9025	45·51	2·80	2·93
1355	51·76	9·05	2·91	10045	45·14	2·43	2·92
1895	51·01	8·30	2·90	11465	44·86	2·15	2·78
2735	50·11	7·40	2·77	22305	43·21	0·50	2·80
3515	49·11	6·40	2·92	24785	43·09	0·38	2·76
4235	48·31	5·60	3·02	" ∞ "	42·71	0·00	—

(Mean 10^5k_2 = 2·88. Corrected for expansion of solvent, 10^5k_2 = 2·95.)

TABLE VIII.

Illustrating determinations of olefin proportions in reactions of secondary alkyl bromides with 1N-*alcoholic sodium ethoxide :* iso*propyl bromide* (*Expt. A*).

(Solvent : EtOH. Temp. 25·0°. Initially [Pr^{i}Br] = 0·1815M and [NaOEt] = 0·9784N. Portions of 10 c.c. used for the estimation of bromide ion and olefin. In the Table the bromide ion is given by the silver, measured in c.c. of 0·0899N-thiocyanate, which survives out of 20 c.c. of added silver nitrate, and the olefin is given by the bromine, measured in c.c. of 0·2556N-thiosulphate, which remains out of 10 c.c. of added standard bromine.)

Initial readings.		Final readings.	
Silver.	Bromine.	Silver.	Bromine.
26·10	25·12, 24·85, 24·80	5·92	13·25, 14·18, 13·65
26·10	24·40, 24·45, 24·60	5·90	14·13, 13·85, 13·45
26·10 (mean)	24·70 (mean)	5·91 (mean)	13·75 (mean)

(Proportion of olefin = 77·1%. Proportion corrected for losses, 82·7%.)

TABLE IX.

Illustrating determinations of first-order rate-constants (k_1 *in sec.*$^{-1}$) *in reactions of secondary alkyl bromides in initially neutral aqueous ethyl alcohol :* iso*propyl bromide* (*Expt. A*).

(Solvent : " 60% " aqueous EtOH. Temp. 80·0°. Initially [Pr^{i}Br] = 0·1341M. In the Table [Pr^{i}Br] is expressed in c.c. of 0·0514N-alkali per 5 c.c. sample.)

t (min.).	[Pr^{i}Br].	10^5k_1.	t (min.).	[Pr^{i}Br].	10^5k_1.
0	13·05	—	184	6·00	7·03
10	12·50	7·14	219	5·20	7·00
20	12·00	6·96	254	4·48	7·01
30	11·48	7·11	314	3·40	7·14
45	10·80	7·00	374	2·70	7·02
59	10·10	7·23	464	1·85	7·01
79	9·24	7·28	554	1·20	7·17
104	8·48	6·90	634	0·85	7·18
144	7·15	6·96	1352	0·40	—

(Mean 10^5k_1 = 7·06.)

TABLE X.

Illustrating determinations of olefin proportions in reactions of secondary alkyl bromides in initially neutral aqueous ethyl alcohol : iso*propyl bromide* (" *Pilot* " *Expt. A*).

(Solvent : " 60% " aqueous EtOH. Temp. 80·0°. Initially [Pr^{i}Br] = 0·1482M. Portions of 10 c.c. taken for estimation of acid and olefin. In the Table the acid is expressed in c.c. of 0·07142N-alkali, and the olefin is given by the bromine, measured in c.c. of 0·1176N-thiosulphate, which survives out of 5 c.c. of added standard bromine.)

	Acid.		Bromine.		Olefin, %.	
t (min.).	Readings.	Mean.	Readings.	Mean.	Uncorr.	Corr.
0	0·50, 0·50	0·50	25·75, 25·35; 25·85, 25·45	25·60	—	—
92	7·18, 7·22	7·20	25·20, 25·50; 24·90, 25·55	25·28	3·90	4·20
142	9·80, 9·90	9·85	24·95, 25·18; 24·80, 25·31	25·06	4·75	5·12
214	12·95, 12·85	12·90	25·50, 25·68; 25·48, 25·27	25·48	0·80	0·87
390	17·10, 17·02	17·06	25·90, 25·35; 25·60, 25·40	25·56	0·19	0·20
1080	21·25, 21·25	21·25	25·80, 25·70; 25·40, 25·60	25·62	—	—

(In consequence of these results, the readings in the main series of experiments were taken initially and after times in the range 90—150 mins. In these experiments portions of 30 c.c. were taken for the olefin estimation in order to increase the accuracy.)

SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Received, January 15th,* 1948.]

---

421. *Mechanism of Elimination Reactions. Part XI. Kinetics of Olefin Elimination from* tert.*-Butyl and* tert.*-Amyl Bromides in Acidic and Alkaline Alcoholic Media.*

By M. L. DHAR, E. D. HUGHES, and C. K. INGOLD.

Data are recorded to show the effect of homology on the rates of the constituent substitutions and eliminations which tertiary alkyl bromides undergo in bimolecular reactions with ethoxide ions, and also in unimolecular reactions in anhydrous ethyl alcohol. In this solvent the unimolecular reactions of tertiary alkyl bromides tend to predominate, and in the present experiments it was not found possible to isolate bimolecular processes; however, it was possible, by the use of considerable concentrations of ethoxide ions, to give them a dominating importance in the total reaction. *tert.*-Butyl and *tert.*-amyl bromides were studied, and the amylenes produced from the latter were analysed, in order to permit the division of the elimination rates and proportions into those parts which apply to the establishment of the double bond in the separate branches of the tertiary alkyl groups.

The bimolecular eliminations of these compounds in ethyl-alcoholic sodium ethoxide proceed considerably more rapidly than do the corresponding reactions of the simpler secondary and primary alkyl bromides; and they proceed too rapidly to permit the measurement of anything

more than limits to the rates of the accompanying bimolecular substitutions. Bimolecular elimination proceeds more rapidly in the *tert.*-amyl than in the *tert.*-butyl group, and rather more than the whole difference is represented by the increased rate of establishment of the double bond in the alkyl branch which becomes lengthened in the *tert.*-amyl group. This is interpreted in Part XVI.

The rate of the overall unimolecular reaction is greater for the *tert.*-amyl than for the *tert.*-butyl compound. The rate of unimolecular substitution is increased, but the proportion of such substitution is decreased, in the higher homologue. The rate, and the proportion, of unimolecular elimination are increased in the amyl compound. The increase of elimination rate is due to a large increase in the rate of establishment of the double bond in the alkyl branch which becomes lengthened, reinforced by smaller increases in the rate at which it enters the branches which remain similar in the two compounds. The increase in the proportion of elimination is the net result of a large increase in the proportion in which the double bond enters the lengthened alkyl branch, partly off-set by notable decreases in the proportions in which it enters the other alkyl branches. The theory of these relationships is given in Part XVI.

THIS paper carries into the field of tertiary alkyl halides our study of constitutional effects on the bi- and uni-molecular reactions of substitution and elimination which alkyl halides may undergo. The general effect of passing from the secondary to the tertiary alkyl series is that the unimolecular mechanisms of both substitution and elimination achieve a much greater relative importance. This is not primarily because the bimolecular reactions of the tertiary halides are slow: the bimolecular eliminations have been found to be faster in the tertiary series than in the secondary. The main cause of the shift of relative importance amongst the mechanisms is that the unimolecular reactions of both substitution and elimination are very much more rapid with tertiary alkyl halides than with secondary.

One effect of this is to remove the uncertainty, which prevailed through part of our study of the series of secondary halides, as to how much of an observed first-order substitution is unimolecular in mechanism and how much is a bimolecular solvolytic process. There is ample evidence that the observed first-order substitutions of tertiary alkyl halides are wholly unimolecular. It is equally definite that the first-order eliminations, which are probably entirely unimolecular even in the secondary alkyl series, are also wholly unimolecular in the tertiary series.

The principal complication which attends the study of the tertiary halides is that, in the hydroxylic solvents employed in this work, we can no longer kinetically isolate the bimolecular reactions from accompanying unimolecular processes. However, we have been able to give to the bimolecular eliminations a sufficient predominance in composite reactions to enable the bimolecular elimination rates to be measured with the requisite accuracy.

As with secondary, so also with tertiary, alkyl halides, different olefins can be formed in suitable cases by elimination along non-equivalent branches of the alkyl chain. The first-order and second-order elimination rates are then composite, and have to be split into the rates of the component simultaneous processes by means of data obtained for the purpose by analysis of the formed mixtures of isomeric olefins.

The tertiary alkyl halides thus studied were *tert.*-butyl and *tert.*-amyl bromides. The former can give but one olefin, *iso*butylene, whilst the latter gives mixtures of amylenes, *viz.*, trimethylethylene and 1-methyl-1-ethylethylene. Anhydrous ethyl alcohol, rather than an aqueous mixture, was employed as solvent, in order to keep the rates of the unimolecular reactions within manageable bounds, and to give as much assistance as possible to the bimolecular processes. Even then the latter could be made to dominate only by the use of considerable concentrations of sodium ethoxide. The temperature throughout the series of measurements was 25·0°.

For each alkyl halide a number of sets of measurements were made. From set to set the initially introduced sodium ethoxide was varied from none to a large excess, the reacting solutions being of three general types, *viz.*, weakly acidic, weakly alkaline, and strongly alkaline. Each set of experiments included at least two types of measurements, *viz.*, that of the total first-order rate-constant, and that of the proportion in which the total reaction produces olefin. The sets of experiments on *tert.*-amyl bromide included also analyses of the mixtures of isomeric olefins generated in each of the three types of solution mentioned above. From the results of these measurements it was possible to extract the required rate-constants.

The results of the measurements of total rates and olefin proportions are given in Table I. The following remarks are necessary in further explanation of the figures. The rates are expressed as first-order rate-constants, and this was always possible, whatever the dominant mechanism, because the concentrations were suitably chosen: the alkali was either absent, so that only unimolecular reactions took place, or it was so dilute that unimolecular reactions

predominated, or it was so concentrated that, although bimolecular reactions predominated, the alkali remained in substantially constant excess, giving rise to first-order reactions. In those olefin estimations which were made in the absence of initially added sodium ethoxide, the usual precautions were taken to avoid loss of formed olefin through acid-catalysed addition of the solvent: the olefin concentrations were measured at various times during the course of a run, and compared with the amounts of total reaction at corresponding times. At the concentrations employed, it was found that the first half-life of the reaction could safely be used for the olefin estimations. In the olefin measurements which were carried out with alkaline solutions, the initial concentration of sodium ethoxide was so adjusted that the mean alkalinity during the production of the measured olefin was the same as the mean alkalinity during the corresponding measurement of the total rate, to the degree of approximation warranted by the limits of accuracy of the olefin determinations. In these runs, the olefin concentration and the total reaction were measured at two times, one near the beginning and one towards the end of the reaction, and the proportion in which the reaction produces olefin was calculated from the differences.

TABLE I.

First-order rate-constants (k_1 *in sec.*$^{-1}$), *and percentages of olefin formed, in the reactions of tertiary alkyl bromides in dry ethyl alcohol, and with ethyl-alcoholic sodium ethoxide in various concentrations, at* 25·0°.

Total reaction rate.			Proportion of olefin.			
Initial [RBr].	Initial [NaOEt].	10^5k_1.	Initial [RBr].	Initial [NaOEt].	% Olefin.	
			tert.-*Butyl bromide.*			
						(mean)
0·10350	0	0·451	0·02061	0	19·0	19·0
0·01709	0·02386	0·522	0·01710	0·0250	25·3	25·9
			0·01454	0·0272	26·4	
0·06397	0·0828	0·637	0·07050	0·1013	44·4	46·1
			0·06980	0·1013	47·7	
0·03837	1·015	3·29	0·09974	1·012	90·0	91·3
			0·08324	1·017	92·6	
0·03837	2·011	4·20	—	—	—	—
			tert.-*Amyl bromide.*			
0·07278	0	1·09	0·03895	0	36·3	36·3
0·01593	0·02313	1·16	0·01577	0·0267	45·9	46·3
			0·02519	0·0266	46·7	
0·06410	0·0848	1·57	0·07380	0·1013	57·8	56·0
			0·09020	0·1013	54·2	
0·03885	1·015	6·24	0·09260	1·012	97·9	98·3
			0·08618	1·014	98·7	
0·03430	2·011	7·02	—	—	—	—

An analysis of these results is contained in Table II. The method is as follows. Each first-order rate-constant, k_1, for the total reaction is split into two component parts, the first-order rate-constants referring to substitution and to elimination, with the aid of the relevant olefin proportion. These first-order substitution and elimination constants are tabulated as $k(S_N1)$ and $k(E1)$, respectively, although these labels are partly misnomers. However, one notices that, for each alkyl halide, the figures for $k(S_N1)$ are independent of the alkali concentration to within the limits of precision set by the least accurate of the measurements, *viz.*, those of the olefin proportions. This shows that these constants are true unimolecular substitution constants, and are correctly labelled $k(S_N1)$. On the other hand, of the first-order elimination constants, tabulated as $k(E1)$, the majority clearly represent the rates of reactions of composite molecularity, and that is why, in the Table, most of these first-order constants are given in parenthesis. Each such constant has a part which is independent of the alkali and a part which depends on the concentration of alkali. Only for the experiments in initially neutral solutions do the first-order elimination constants represent true unimolecular constants, correctly labelled $k(E1)$. In the other cases, that part of the first-order rate which depends on the alkali is evidently due to a process of bimolecular elimination. It follows that, by dividing the increase in the first-order elimination constant, resulting from the addition of alkali, by the

mean concentration of alkali, one can arrive at the bimolecular elimination rate-constant $k(E2)$. The values of this constant, given in Table II, were obtained by first deriving constants thus, and then correcting them for the change in volume of the solvent between the temperature at which the solutions were prepared for the rate measurements and the temperature of the reactions themselves. The values of these bimolecular constants can be seen to fall notably at the highest concentrations (1N and 2N) of alkali, and this is undoubtedly a salt-effect. The bimolecular eliminations, as well as the bimolecular substitutions, by anionic reagents, of alkyl halides should exhibit substantial negative salt-effects, owing to the spreading of the anionic charge in the transition state of reaction (cf. Dostrovsky, Hughes, and Ingold, this vol., p. 1283). In fact, such salt-effects are known for the bimolecular substitutions and eliminations of primary and secondary alkyl bromides (Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 899); and they are of just the same order of magnitude as the effects now found for the bimolecular eliminations of tertiary alkyl bromides.

TABLE II.

Analysis of kinetic data for the reactions of tertiary alkyl bromides in ethyl alcohol and with ethyl-alcoholic sodium ethoxide at 25·0°, showing the rate-constants [k_1, $k(S_N1)$ *and* $k(E1)$ *in sec.*$^{-1}$, *and* $k(E2)$ *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*] *of the constituent reactions.*[1]

Mean [NaOEt].	10^5k_1.	% Olefin.	$10^5k(S_N1)$.	$10^5k(E1)$.	$10^5k(E2)$.
		tert.-*Butyl bromide.*			
0	0·451	19·0	0·365	0·086	—
0·0153	0·522	25·9	0·387	(0·135)	~3·4 [3]
0·0508	0·637	46·1	0·344	(0·293)	4·17
0·996	3·29	91·3	~0·29 [3]	(3·00)	3·00
1·992	4·20	93·2 [4]	~0·38 [3]	(3·91)	1·97
		tert.-*Amyl bromide.*			
0	1·09	36·3	0·695	0·395	—
0·0152	1·16	46·3	0·623	(0·537)	9·6
0·0527	1·57	56·0	0·690	(0·880)	9·44
0·996	6·24	98·3	—	(6·13)	5·90
1·994	7·02	98·6 [4]	—	(6·92)	3·27

[1] The bimolecular substitution constant $k(S_N2)$ is too small to be extracted from the measurements, but the estimated errors in the olefin proportions allow the following upper limits to be deduced: for *tert.*-butyl bromide $k(S_N2) < 0·1 \times 10^{-6}$, and for *tert.*-amyl bromide $k(S_N2) < 0·2 \times 10^{-6}$ sec.$^{-1}$ g.-mol.$^{-1}$ l.

[2] Value rendered inaccurate by its dependence on the small difference between the two percentages 19·0 and 25·9% of olefin.

[3] Values rendered uncertain by their dependence on the differences from 100 of the high olefin percentages 91·3 and 93·2%.

[4] Calculated from the rate-constants and the other percentages of olefin for the same alkyl halide.

The determinations of the separate amylenes in the mixture of isomerides liberated from *tert.*-amyl bromide required quantities of olefin such that certain precautions had to be taken. In all cases the alkyl halide was initially 0·85—0·88M. If the experiment in acid solution had been conducted in the usual way, there would have been an equivalent generation of hydrogen bromide, which would have induced acid-catalysed solvent-addition to the olefins, and might have done so in such a way as to disturb the proportions. The method was therefore to add an indicator, and to prevent the solution from becoming more than weakly acid by the frequent addition of small amounts of alcoholic sodium ethoxide during the run. In the experiment in dilute alkaline solution, it was obviously inadmissable to add an equivalent of sodium ethoxide initially, and therefore, here again, an indicator was used, and small amounts of alcoholic sodium ethoxide were added at sufficiently frequent intervals to maintain the solution only very weakly alkaline. In the experiment in strongly alkaline solution an initially added excess of sodium ethoxide was used. In each case the olefins from the complete reaction were collected, freed from non-isomeric impurities, and analysed by the measurement of refractive index. The experimental results are in Table III.

By the use of the rate data in Table II, it is readily possible to extract from the result in Table III the proportions in which the isomeric olefins are produced by each of the two mechanisms of eliminations. These proportions, as well as the rate-constants of the four component reactions by which the two olefins are produced by the two mechanisms, are given in Table IV.

TABLE III.

Composition of amylenes obtained from tert.*-amyl bromide by reaction in ethyl alcohol and with ethyl-alcoholic sodium ethoxide at 25·0°.*

Expt. no.	[Am^{t}Br] initial.	[NaOEt]. Initial.	[NaOEt]. Mean.	% $Me_2C{:}CHMe$.	% $MeEtC{:}CH_2$.
1	0·882	(None : solution weakly acid)		81·6	18·4
2	0·854	Very dilute	Very dilute	81·7	18·3
3	0·855	2·05	1·62	71·9	28·1

TABLE IV.

Compositions of amylenes produced by bi- and uni-molecular elimination from tert.*-amyl bromide in ethyl alcohol at 25°. Rate-constants* [k(E2) *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*; k(E1) *in sec.*$^{-1}$] *of the component processes of elimination.*

Mechanism.	Percentages. $Me_2C{:}CHMe$.	Percentages. $MeEtC{:}CH_2$.		Rate-constants.* $Me_2C{:}CHMe$.	Rate-constants.* $MeEtC{:}CH_2$.
*E*2	71·1	28·9	$10^5k(E2)$	6·72	2·72
*E*1	81·7	18·3	$10^5k(E1)$	0·323	0·072

* Ionic strengths in the neighbourhood 0·05.

We now collect corresponding results for *tert.*-butyl and *tert.*-amyl bromide, not only to show the effects of homology in these examples, but also to facilitate comparison with the analogous data for primary and secondary alkyl halides, given in the two preceding papers. In Table V the rate-constants for the bimolecular eliminations undergone by the two tertiary halides are given both in their collective form and with respect to elimination along each of the three branches of the tertiary alkyl chain. In Table VI the kinetic data for unimolecular substitution and elimination are similarly compared, with such particulars as are demanded by the circumstance that these reactions have two stages, both requiring consideration.

TABLE V.

Comparison of rate-constants [k(E2) *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*] *for bimolecular elimination from tertiary alkyl bromides in ethyl-alcoholic sodium ethoxide at 25°.*

Alkyl halide.	$10^5k(E2)$ ([NaOEt] ~0·05). Total.	Per branch.	$10^5k(E2)$ ([NaOEt] ~1·0). Total.	Per branch.
CH_3, CH_3, CH_2>CBr	4·17	1·39 1·39 1·39	3·00	1·00 1·00 1·00
$CH_3{\cdot}CH_2$, CH_3, CH_2>CBr	9·44	6·72 1·36 1·36	5·90	4·20 0·85 0·85

We direct attention to the following points. The figures for the rates of bimolecular elimination from alkyl bromides (Table V) show that elimination proceeds more rapidly from the *tert.*-amyl than from the *tert.*-butyl group, and that the increase is due entirely to the increased rate of establishment of the olefinic double bond in that alkyl branch which becomes lengthened in the tertiary amyl group. As to the unimolecular reactions, the rate of the overall reaction is greater for the *tert.*-amyl compound than for the lower homologue. The rate of the unimolecular substitution is increased, but the proportion of unimolecular substitution is decreased, in the higher homologue. The rate of unimolecular elimination is also greater for *tert.*-amyl than for *tert.*-butyl bromide; and this result is due to a large increase in the rate of formation of the double bond in that alkyl branch which becomes lengthened in the tertiary amyl compound, reinforced by small increases in the rate at which it enters the alkyl branches

TABLE VI.

Comparison of rate constants [k_1, $k(S_N1)$ *and* $k(E1)$ *in sec.*$^{-1}$] *and olefin proportions in unimolecular substitutions and eliminations of tertiary alkyl bromides in ethyl alcohol at 25°.*

Alk in AlkBr.	10^5k_1.	$10^5k(S_N1)$.	$10^5k(E1)$. Total.	$10^5k(E1)$. Per branch.	% Subn.	% Elimination. Total.	% Elimination. Per branch.
	0·45	0·365	0·086	0·029 0·029 0·029	81·0	19·0	6·3 6·3 6·3
	1·09	0·695	0·395	0·323 0·036 0·036	63·7	36·3	29·6 3·3 3·3

which remain similar in both compounds. The proportion of unimolecular elimination is likewise greater for *tert.*-amyl than for *tert.*-butyl bromide; but this is the net result of a big increase in the proportion in which the double bond enters the lengthened alkyl branch of the *tert.*-amyl group, partly off-set by marked decreases in the proportion in which it becomes established in these alkyl branches which remain similar in the two homologues. The theory of these relationships will be discussed in Part XVI.

EXPERIMENTAL.

Materials.—*tert.*-Butyl and *tert.*-amyl alcohols were converted into their bromides by shaking with concentrated aqueous hydrogen bromide at room temperature. After being dried with potassium carbonate, the products had the respective b. p.s 74°/756 mm. and 106°/756 mm.

Method of Kinetic Measurements.—In the experiments in initially neutral or dilute alkaline solution, the samples for analysis were withdrawn from the solution in bulk, which was contained in a stoppered measuring flask immersed in the thermostat. The acid or alkaline samples, usually 5 c.c., were run into 100 c.c. of well-cooled acetone or ethyl alcohol, and titrated with standard alkali or acid, lacmoid being used as indicator. Experiments in the more strongly alkaline media were conducted by the sealed-bulb method, and the determination of residual alkali was replaced by a determination of the liberated halide ion by Volhard's method. In the experiments in initially neutral solution, the " infinity " titres were obtained after dilution with water, in order to eliminate any error in these quantities arising from the slight reversibility of alcoholysis. In all cases first-order rate-constants were calculated from the expression $k_1 = (1/t)\log_e a/(a - x)$, where t is the time in seconds, a is the initial concentration of the alkyl bromide, and x is its concentration at time t.

Method for Olefin Proportions.—The extraction method was used (cf. the two immediately preceding papers.)

Method for Analysis of Amylene Mixtures.—Pure specimens of trimethylethylene and 1-methyl-1-ethylethylene were obtained, the first from a commercial sample by careful distillation through an efficient column, and the second from 2-methyl-*n*-butyl alcohol by way of the bromide. They had the refractive indices $n_D^{20°}$ 1·38774 and $n_D^{20°}$ 1·37774, respectively, in close agreement with the values reported by Sherrill and Walter (*J. Amer. Chem. Soc.*, 1936, **58**, 742); and the refractive indices of mixtures fitted a linear interpolation formula. The reaction mixtures from which the olefin was to be collected for analysis, were diluted with water; and the olefin was then isolated by distillation, washed with water, dried, and distilled. Its refractive index was measured, and its composition therefrom deduced.

Results of Measurements.—The principal numerical results are given in Tables I and III. The different types of measurement are illustrated by more detailed records contained in Tables VII—XII.

TABLE VII.

Illustrating determinations of first-order rate-constants (k_1 *in sec.*$^{-1}$) *of the reactions of tertiary alkyl bromides with initially neutral ethyl alcohol :* tert.*-butyl bromide.*

(Solvent: EtOH. Temp. 25·0°. Initially [Bu^{t}Br] = 0·1035M. In the Table [Bu^{t}Br] is expressed in c.c. of 0·03449N-alkali per 5 c.c. sample.)

t (min.).	[Bu^{t}Br].	10^5k_1.	t (min.).	[Bu^{t}Br].	10^5k_1.
0	15·01	—	1,859	9·09	4·49
104·4	14·59	4·52	2,070	8·59	4·49
274·0	13·95	4·50	3,057	6·42	4·63
428·3	13·40	4·41	4,706	4·15	4·55
598·9	12·83	4·37	5,874	2·90	4·66
1339	10·49	4·46	7,360	1·90	4·67
1376	10·34	4·51	10,080	1·05	4·40
1616	9·69	4·51			Mean 4·51

TABLE VIII.

Illustrating determinations of olefin proportions in reactions of tertiary alkyl bromides in initially neutral ethyl alcohol: tert.*-amyl bromide.*

(Solvent: EtOH. Temp. 25·0°. Initially [Am^{t}Br] = 0·03895M. Portions of 20 c.c. taken for estimation of acid and olefin. In the Table the acid is expressed in c.c. of 0·02513N-alkali, and the olefin is given by the bromine, measured in c.c. of 0·05128N-thiosulphate, which remains out of 10 c.c. of added standard bromine.)

	Acid.		Bromine.		
t (min.).	Readings.	Mean.	Readings.	Mean.	Olefin, %.
0	0·60, 0·60	0·60	12·85, 12·90, 12·88	12·87	—
295	5·40, 5·50	5·45	11·00, 11·00, 11·40	11·13	36·6
345	6·80, 6·80	6·80	10·70, 10·60, 10·65	10·65	36·5
510	8·55, 8·45	8·50	9·95, 9·85, 10·15	9·98	37·3
870	12·65, 12·65	12·65	8·45, 8·90, 8·60	8·65	35·8
1200	15·70, 15·80	15·75	7·65, 7·75, 7·60	7·66	35·1
					Mean 36·3

TABLE IX.

Illustrating determinations of first-order rate-constants (k_1 *in sec.*$^{-1}$) *in reactions of tertiary alkyl bromides with dilute ethyl alcoholic sodium ethoxide:* tert.*-butyl bromide.*

(Solvent: EtOH. Temp. 25°. Initially [Bu^{t}Br] = 0·01709M and [NaOEt] = 0·02386N. In the Table [Bu^{t}Br] is expressed in c.c. of 0·0211N-acid per 10 c.c. sample.)

t (min.).	[Bu^{t}Br].	10^5k_1.	t (min.).	[Bu^{t}Br].	10^5k_1.
0	8·10	—	1470	5·10	5·23
161·6	7·70	5·22	1871	4·45	5·33
276·2	7·43	5·21	2863	3·16	5·48
391·3	7·18	5·14	3300	2·75	5·45
506·5	6·95	5·04	4516	2·05	5·07
1296	5·38	5·26	6103	1·20	5·31
					Mean 5·22

TABLE X.

Illustrating determinations of first-order rate-constants (k_1 *in sec.*$^{-1}$) *in reactions of tertiary alkyl bromides with concentrated alcoholic sodium ethoxide:* tert.*-butyl bromide.*

(Solvent: EtOH. Temp. 25°. Initially [Bu^{t}Br] = 0·03837M and [NaOEt] = 1·015N. In the Table [Bu^{t}Br] is expressed in c.c. of 0·0234N-thiocyanate.)

t (min.).	[Bu^{t}Br].	10^5k_1.	t (min.).	[Bu^{t}Br].	10^5k_1.
0	8·20	—	268·0	4·95	3·14
51·5	7·39	3·36	344·5	4·20	3·24
80·6	6·97	3·36	404·6	3·80	3·16
120·0	6·44	3·35	484·3	3·00	3·46
159·6	6·00	3·26	523·5	2·90	3·31
228·0	5·20	3·33	577·4	2·65	3·26
					Mean 3·29

TABLE XI.

Illustrating determinations of olefin proportions in reactions of tertiary alkyl bromides with ethyl-alcoholic sodium ethoxide: tert.*-butyl bromide (Expt. A).*

(Solvent: EtOH. Temp. 25·0°. Initially [Bu^{t}Br] = 0·09974M and [NaOEt] = 1·0121N. Portions of 20 c.c. used for estimations of bromide ion and olefin. In the Table the bromide ion is given by the silver, measured in c.c. of 0·07333N-thiocyanate, which remains out of 10 c.c. of added standard silver nitrate, and the olefin is given by the bromine, measured in c.c. of 0·09737N-thiosulphate, which survives out of 10 c.c. of added standard bromine.)

Initial readings.		Final readings.	
Silver.	Bromine.	Silver.	Bromine.
29·80	47·15, 47·01, 47·15	2·55	10·95, 11·60, 11·00
29·80	47·10, 47·20	2·65	11·20, 11·10, 11·05
29·80 (mean)	47·20, 47·10	2·60	11·20, 11·25
	47·13 (mean)	2·60 (mean)	11·16 (mean)

Proportion of olefin = 87·8%. Corrected for losses = 90·0%.

TABLE XII.

Particulars of experiments on the composition of the mixture of amylenes obtained from tert.*-amyl bromide by reaction in acidic or alkaline ethyl alcohol.*

Initial Am^tBr (g.).	Initial EtOH (c.c.).	[NaOEt].	Time at 25° (hrs.).	Yield, olefins (g.).	$n_D^{20°}$.
200	1500	None: just acid	146	—[1]	1·38590
155	1200	Just alkaline	130	30	1·38591
155	1200	2·05N[2]	12	70·5	1·38493

[1] Yield not measured.
[2] Initial value.

SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Received, January 15th,* 1948.]

422. *Mechanism of Elimination Reactions. Part XII. Kinetics of Olefin Eliminations from Ethyl-,* n*-Propyl-,* n*-Butyl,* iso*Butyl-, and 2-Phenylethyl-dimethylsulphonium Salts in Alkaline Alcoholic Media.*

By E. D. HUGHES, C. K. INGOLD, and G. A. MAW.

Data are recorded to show the effects of certain constitutional changes on the rates of the substitutions and eliminations which primary alkyl-dimethylsulphonium ions undergo in bimolecular reactions with ethoxide ions in anhydrous ethyl alcohol as solvent. The structural effects studied are those of increasing chain length, of successively introduced β-linked methyl substituents, and of a β-phenyl substituent.

The substitutions are composite, since either methyl or the higher alkyl group may be displaced from the sulphonium ion in the bimolecular substitution. In the case of the dimethyl-2-phenylethylsulphonium ion, which shows an outstandingly large rate of total bimolecular substitution, an analysis of products was made which allows the total substitution rate to be divided into its components. It is thus shown that the increase of substitution rate caused by the phenyl substituent is due mainly to the increased rate of displacement of the 2-phenylethyl group itself, and not to any effect of this phenylated group on the rate of displacement of a methyl group. This effect of the phenyl substituent is regarded as essentially polar.

The bimolecular eliminations are simple reactions. Their rates fall with increasing length of the alkyl chain, fall on the introduction of β-linked methyl substituents, and show a striking rise on the introduction of a β-phenyl substituent. These effects, which are considered theoretically in Part XVI, show some marked contrasts with those displayed by the corresponding reactions of primary alkyl bromides.

THIS paper records the first part of a systematic study by kinetic methods of the effect of chemical constitution on the facility of olefin elimination from alkylsulphonium ions. As with the olefin-forming reactions of alkyl halides, so also with those of alkylsulphonium ions, nucleophilic substitutions usually accompany the eliminations (in the following formulæ the R's need not be identical):

$$R_2CH{\cdot}CR_2{\cdot}\overset{+}{S}R_2 \xrightarrow{\bar{X}} \begin{cases} R_2CH{\cdot}CR_2X + SR_2 & (S_N) \\ HX + R_2C{:}CR_2 + SR_2 & (E) \end{cases}$$

It is also just as true for the decompositions of alkylsulphonium ions as it is for those of alkyl halides, that the concurrent reactions of substitution and elimination can each pursue either of two mechanisms, *viz.*, the bi- and uni-molecular mechanisms which we label S_N2 and S_N1 for substitution and $E2$ and $E1$ for elimination. Thus, in the general case, four component reactions have to be distinguished and separately considered with respect to the effect of alkyl structure on their rates:

$$R_2CH{\cdot}CR_2{\cdot}\overset{+}{S}R_2 \begin{cases} \xrightarrow{\bar{X}} \begin{cases} R_2CH{\cdot}CR_2X + SR_2 & (S_N2) \\ HX + R_2C{:}CR_2 + SR_2 & (E2) \end{cases} \\ \xrightarrow[\text{slow}]{} R_2CH{\cdot}\overset{+}{C}R_2 + SR_2 \xrightarrow[\text{fast}]{\bar{X}} \begin{cases} R_2CH{\cdot}CR_2X + SR_2 & (S_N1) \\ HX + R_2C{:}CR_2 + SR_2 & (E1) \end{cases} \end{cases}$$

Kinetic analyses involving all these reactions will be described in the present group of papers. In this paper we are concerned with a series of sulphonium ions in which the alkyl radical,

represented in the above general formulæ by $R_2CH{\cdot}CR_2{\cdot}$, is a primary radical of the form $R_2CH{\cdot}CH_2{\cdot}$, where either R may be H, Me, Et, or Ph. For such primary alkylsulphonium ions chief importance attaches to the bimolecular mechanisms of substitution and elimination; and by operating with ethoxide ions as the reagent, and in dry ethyl alcohol as the solvent, we can arrange that these reactions, S_N2 and $E2$, shall take exclusive control:

$$R_2CH{\cdot}CH_2{\cdot}\overset{+}{S}R_2 + \bar{O}Et \longrightarrow \begin{cases} R_2CH{\cdot}CH_2{\cdot}OEt + SR_2 & (S_N2) \\ HO{\cdot}Et + R_2CH{:}CH_2 + SR_2 & (E2) \end{cases}$$

Each component reaction thus exhibits second-order kinetics, and hence the overall reaction is of this kinetic form.

Second-order kinetics for bimolecular elimination ($E2$) from sulphonium ions has been previously established in the following cases. (1) The overall decomposition of dithian methohydroxide, $\{S<[CH_2{\cdot}CH_2]_2>SMe\}^+OH^-$, in water was shown by Green and Sutherland to be a reaction of the second order (*J.*, 1911, **99**, 1174), Mansfield (*Ber.*, 1886, **19**, 696, 2658) and V. Meyer (*ibid.*, p. 3262) having previously proved that the main product of the reaction is the ethylene derivative, $MeS{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH{:}CH_2$. (2) Hughes and Ingold showed that trimethyl-2-phenylethylammonium hydroxide in aqueous solution yielded styrene by a reaction of the second order (*J.*, 1933, 523). (3) The same authors established that, in the aqueous decomposition of dimethyl-*tert.*-butylsulphonium hydroxide, $\{SMe_2Bu^t\}^+OH^-$, *iso*butylene is formed mainly by a reaction of the second order ($E2$), even though the accompanying substitution, which produces *tert.*-butyl alcohol, is a reaction of the first order (S_N1) (*J.*, 1933, 1571). (4) Gleave, Hughes, and Ingold established that formation of ethylene by the decomposition of triethylsulphonium hydroxide in water or aqueous alcohol is a second-order process (*J.*, 1935, 235). (5) Similar kinetics were established for the production of propylene by the decomposition of methyldi*iso*propylsulphonium hydroxide in aqueous alcohol (*idem*, *ibid.*).

The sulphonium ions now studied were all of the type alkyl-dimethylsulphonium, $Alk\overset{+}{S}Me_2$, the variable group Alk being chosen in order to illustrate the following three types of progressive structural change. (Series 1.) The series Alk = ethyl, *n*-propyl, *n*-butyl illustrates effects due to the progressive lengthening of the alkyl chain. (Series 2.) The series ethyl, *n*-propyl, *iso*butyl illustrates the effect of successively introduced β-linked methyl groups up to the limit set by the necessity of retaining one β-hydrogen atom. (Series 3.) The series ethyl, *n*-propyl, 2-phenylethyl shows the relative magnitude of effects attributable to the capacity for hyperconjugation displayed by the terminal methyl group of *n*-propyl and to the power of ordinary conjugation possessed by the phenyl group in 2-phenylethyl.

The reactions of the iodides of all these sulphonium ions with sodium ethoxide in ethyl alcohol were studied at 63·9°. They show, as they should, a negative salt effect, a detailed investigation of which will be published later. For the purpose of our structural comparisons we have therefore used approximately the same initial concentrations in all cases, *viz.*, 0·05M-sulphonium iodide and 0·095M-sodium ethoxide. We find in each case two second-order reactions, S_N2 and $E2$. The first-order reactions S_N1 and $E1$ do not become appreciable in any of the examples treated. Our procedure was therefore to measure the rate constant, k_2, of the total second-order reaction, $S_N2 + E2$, by following the loss of alkali, and then to divide it into its components, $k(S_N2)$ and $k(E2)$, on the basis of a measurement of the proportion in which olefin is produced. The proportion should, of course, remain constant through the course of the change; and it was in fact shown to do so, such a demonstration being possible in these alkaline conditions, because the olefins, when once formed, do not become destroyed by interaction with the solvent, as they do in acidic solutions. The constancy of the olefin proportion with time having been shown, further measurements of the olefin proportion were usually made towards the end of reaction, for the sake of the greater accuracy thus attainable.

Table I contains the main series of measurements of the total bimolecular rate-constants, and of the proportions in which olefin is formed, in the reactions of the alkyl-dimethylsulphonium ions. In Table II these data are analysed in terms of the rate-constants of the individual bimolecular reactions of substitution and elimination, S_N2 and $E2$.

The two rate-constants $k(S_N2)$ and $k(E2)$ collectively represent three simultaneous reactions, because there are two possible directions of substitution:

$$Alk{\cdot}\overset{+}{S}Me_2 + \bar{O}Et \longrightarrow \begin{cases} Me{\cdot}OEt + Alk{\cdot}SMe \\ Alk{\cdot}OEt + SMe_2 \end{cases} \quad (S_N2)$$
$$HOEt + Olefin + SMe_2 \quad (E2)$$

TABLE I.

Second-order rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*) *and percentages of olefin formed in the reactions of primary alkyl-dimethylsulphonium iodides with sodium ethoxide in dry ethyl alcohol at* 63·95°.

(Initially [$AlkSMe_2I$] ~0·05 and [NaOEt] ~0·095 in all cases.)

Alk in $(Alk\overset{+}{S}Me_2)\bar{I}$.	10^5k_2.		% Olefin.	
	Individual values.	Mean.	Individual values.	Mean.
Ethyl	400, 386, 380	389	{14·8, 15·6, 15·1 15·8, 15·2, 15·6}	15·4
n-Propyl	371, 392, 380	381	6·8, 7·1, 7·4	7·1
n-Butyl	391, 396	394	4·3, 3·8, 4·6, 4·5	4·3
*iso*Butyl	593, 593	593	2·6, 2·4, 2·3	2·4
2-Phenylethyl	—	28,800 *	{88·8, 89·4, 90·0 88·6, 90·2}	89·4

* Extrapolated from the following results at lower temperatures, *viz.*,

10^5k_2 = 1050, 1050 (Mean, 1050) at 35·05° (T = 308·20°)
,, = 3960, 3990 (,, , 3985) ,, 45·92° (T = 319·07°)

by means of the derived equation

$$\log_{10}k_2 = 14{\cdot}98 - 23{,}900/(2{\cdot}303 \times 1{\cdot}986 \times T).$$

TABLE II.

Analyses of kinetic data for the reactions of alkyl-dimethylsulphonium iodides with sodium ethoxide in ethyl alcohol at 64°, *showing the variation in the rates of bimolecular substitution and elimination with progressive changes in the structure of the alkyl group.*

Series.	Alkyl group.	10^5k_2.	% Olefin.	$10^5k(S_N2)$.	$10^5k(E2)$.
1	$CH_3{\cdot}CH_2{\cdot}$	389	15·4	329	60
	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}$	381	7·1	354	27
	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}$	394	4·3	377	17
2	$CH_3{\cdot}CH_2{\cdot}$	389	15·4	329	60
	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}$	381	7·1	354	27
	$(CH_3)_2CH{\cdot}CH_2{\cdot}$	593	2·4	579	14
3	$CH_3{\cdot}CH_2{\cdot}$	389	15·4	329	60
	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}$	381	7·1	354	27
	$C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}$	28,800	89·4	3050	25,750

It used to be assumed that, in the alkaline aqueous decompositions of sulphonium ions of the type $Alk\overset{+}{S}Me_2$, the group Alk is eliminated exclusively as olefin, whilst any alcohol simultaneously produced is methyl alcohol. However, Ingold and Kuriyan showed (*J.*, 1933, 991) that, when Alk is ethyl or *n*-propyl, appreciable amounts of ethyl or *n*-propyl alcohol are formed, along with the ethylene or propylene, and the methyl alcohol. Accordingly, we may surely expect that, in alkaline ethyl-alcoholic solutions, ethyl alkyl ethers will be produced, as well methyl ethyl ether, and, of course, the olefins. Thus the observed variations in the, rate-constant $k(S_N2)$ as the group Alk is changed will be due in part to differences in the rate at which this group itself is displaced in bimolecular substitution, and in part to the effect of different alkyl groups on the rate at which a methyl group is displaced in substitution. Owing to experimental difficulties, we have not yet secured any systematic data which would enable these two effects to be distinguished; but an approximate analysis of the matter has been made in one case. This is that of the 2-phenylethyl compound, for which the substitution rate is notably greater than for any of the purely aliphatic compounds. Most of this increase is found to be due to an increased rate of displacement in substitution of the 2-phenylethyl group itself. Direct analysis of the reaction product has given the proportion of styrene as 89·4%, and the proportion of dimethyl sulphide as 98·5%. It follows that ethyl 2-phenylethyl

ether must be produced to the extent of 9%. The production of methyl ethyl ether is estimated either as 1·5% by difference, or as 3% on the basis of a difficult determination of the methyl 2-phenylethyl sulphide. On either figure, the 2-phenylethyl group is displaced by substitution several times more rapidly than is the methyl group from the same compound, and several times more rapidly than is methyl or any of the higher alkyl groups from the purely aliphatic sulphonium compounds. We interpret this as a polar effect within the 2-phenylethyl group, in which the phenyl group, as usual, accommodates itself to the electrical requirements of the reaction.

Concerning the elimination rates, we restrict ourselves here to pointing out the facts. They are that the bimolecular rate falls with increasing length of the alkyl chain, and falls on the introduction of β-linked methyl substituents, but rises strikingly on the introduction of a β-phenyl substituent. The first two of these effects present marked contrasts with those exhibited by the bimolecular elimination rates of the primary alkyl halides (Part IX). With these compounds the rate at first rises sharply, and then falls slowly, with increasing length of the alkyl chain; and it rises with the successive introduction of β-linked methyl substituents. It rises strikingly on the introduction of a β-phenyl substituent; in this the alkyl halides and sulphonium ions resemble each other. A theoretical discussion of all these relations will be given in Part XVI.

Experimental.

Materials.—The required sulphonium iodides were not prepared by the apparently easy method of direct addition of alkyl iodides to dimethyl sulphide, because this method often leads to the formation in appreciable quantities of trimethylsulphonium iodide, an impurity difficult to remove. The preparations therefore started from the alkylthiols, and proceeded by way of the methyl alkyl sulphides, to which methyl iodide was finally added. The crude salts, which were often sticky and yellow at first, were washed with dry ether, dissolved in warm absolute ethyl alcohol, and cooled in solution to −80° until crystals began to be formed. Crystallisation was furthered by the slow addition of pre-cooled, dry ether, the solvent being then poured off, and the whole process was repeated until all visible colour had disappeared. The crystals were collected out of contact with moist air, and kept over phosphoric oxide. All the salts, except dimethyl-2-phenylethylsulphonium iodide, were extremely deliquescent, and vacuum weighing bottles were therefore used for their analysis. The iodide-ion content was determined as an indication of purity: Dimethylethylsulphonium iodide gave I = 58·16% (Calc., 58·20%); dimethyl-*n*-propylsulphonium iodide gave I = 54·49% (Calc., 54·69%); dimethyl-*n*-butylsulphonium iodide gave I = 51·58% (Calc., 51·58%); dimethyl*iso*butylsulphonium iodide gave I = 51·69% (Calc., 51·58%); dimethyl-2-phenylethylsulphonium iodide, m. p. 129°, gave I = 43·00% (Calc., 43·17%).

The ethyl alcohol required for the kinetic measurements was prepared by drying commercial "absolute" alcohol with the aid of sodium and ethyl phthalate (Smith, *J.*, 1927, 1288; Manske, *J. Amer. Chem. Soc.*, 1931, **53**, 1106).

Method of Kinetic Measurements.—Portions, usually 5 c.c., of the reaction mixture, taken from a standard measuring flask, were enclosed in the cold in sealed tubes, which were placed in the thermostat for known times and then treated by one of the following methods. The tubes after being chilled were either broken under 100 c.c. of cold acetone, the alkali being then determined by means of 0·02N-sulphuric acid, with lacmoid as the indicator; or they were broken under 100 c.c. of ice-cold water, and titrated as before, but with a mixture of equal parts of cresol-red and thymol-blue as indicator. The original solution was made up only approximately by weighing: its exact composition was deduced from readings made on two tubes which were left in the thermostat for ten times the period of half-change of the reaction. All other tubes were shaken for two minutes when first put into the thermostat, the end of the two-minute period being treated as the time-zero of the reaction being investigated. Second-order rate-constants were calculated from the formula $k_2 = \{1/t(a-b)\}\log_e\{b(a-x)/a(b-x)\}$, when t is the time in seconds, and a and b are the initial concentrations of sodium ethoxide and alkyldimethylsulphonium iodide respectively, and x is the concentration of alkali destroyed at time t. The constants thus obtained were corrected for the change in volume of the solvent between the temperature at which the solutions were made up and the temperature of the thermostat.

A special method of making up solutions had to be employed in the case of dimethyl-2-phenylethylsulphonium iodide, owing to its low solubility in ethyl alcohol at 0°. The iodide was dissolved in half the total amount of alcohol at 46°, and portions of 2·5 c.c. of this solution were run into portions of 2·5 c.c. of alcohol containing the requisite amount of sodium ethoxide cooled to 0°. (Allowance was made for thermal expansion when measuring volumes at 46°.) The sulphonium iodide crystallised while the tubes were being sealed, but it redissolved completely while they were being shaken for the initial two minutes in the thermostat. The kinetics of the reaction could then be followed as usual.

Methods for Olefin Estimation.—Ethylene and propylene were estimated by the aspiration method (Hughes, Ingold, and Shapiro, *J.*, 1936, 225), and *n*-butylene, *iso*butylene, and styrene by the extraction method (Hughes Ingold, Masterman, and MacNulty, *J.*, 1940, 899), organic sulphides being removed, in either case, with the aid of saturated aqueous mercuric chloride (cf. Part VI, this vol., p. 2042), before the olefin was determined by uptake of bromine.

Results of Measurements.—The results of the main series are summarised in Table I. Their experimental basis is illustrated in Tables III, IV, and V. Table III records the first of the three rate measurements at 63·95° on dimethylethylsulphonium iodide, and Tables IV and V the first two of the six olefin estimations made with this substance. The first of the olefin estimations shows that the proportion

in which olefin is formed remains constant during the reaction. The second olefin experiment is of the same type as all the subsequent ones, and is concerned with the amount of olefin in the product of the completed reaction.

The reaction with the dimethyl-2-phenylethylsulphonium salt went too quickly at 63·95° to be measured with accuracy. The proportion of olefin in the completed reaction at this temperature was determined, but it was not directly proved in this case that the proportion remained constant throughout reaction. The rate of the overall reaction at 63·95° was obtained by extrapolation from measurements at lower temperatures, the particulars of which are given in the footnote beneath Table I.

Some further measurements have been made, which are not included in Table I, because they relate to conditions other than those to which the data of Table I apply. One group of these additional results has already been partly quoted in Part VIII (this vol., p. 2049), and the main particulars of the experiments are therefore now recorded. They are in Table VI. Some further measurements of a generally similar kind will be included in a later paper dealing with salt effects on sulphonium salt decompositions.

TABLE III.

Illustrating determinations of total second-order rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*) : *dimethylethylsulphonium iodide* (*Expt. A*).

(Solvent : EtOH. Temp. 63·95°. Initially [SMe_2EtI] = 0·0494M and [NaOEt] = 0·0966N. In the Table [SMe_2EtI] and [NaOEt] are each expressed in c.c. of 0·02134N-acid per 5 c.c. sample.)

t (min.).	[NaOEt].	[SMe_2EtI].	10^3k_2.	t (min.).	[NaOEt].	[SMe_2EtI].	10^3k_2.
0	22·55	11·53	—	42	16·37	5·35	3·76
4	21·29	10·27	—	46	16·03	5·01	3·78
12	20·10	9·08	3·64	51	15·72	4·70	3·71
20	18·85	7·83	3·67	55	15·46	4·44	3·70
24	18·29	7·27	3·70	59	15·14	4·12	3·77
30	17·54	6·52	3·75	63	14·96	3·94	3·72
34	17·13	6·11	3·74	67	14·68	3·66	3·74
38	16·72	5·70	3·76	∞	11·02	—	—

(Mean $k_2 = 3·73 \times 10^{-3}$ sec.$^{-1}$ g.-mol.$^{-1}$ l.; corrected for solvent expansion, $k_2 = 4·00 \times 10^{-3}$ sec.$^{-1}$ g.-mol.$^{-1}$ l.)

TABLE IV.

Illustrating determinations of olefin designed to show that the proportion is constant throughout reaction : ethylene from dimethylethylsulphonium iodide by the aspiration method (*Expt. A*).

(Solvent : EtOH. Temp. 63·95°. Initially [SMe_2EtI] = 0·0520M and [NaOEt] = 0·0965N. Pairs of tubes were withdrawn from the thermostat at the zero of time, after one-third, after two-thirds, and after the completion, of the reaction. One tube of each pair was used to estimate loss of alkali, and the other the formation of ethylene. In the Table [SMe_2EtI] and [NaOEt] are each expressed in c.c. of 0·02284N-acid per 5 c.c. sample, whilst the bromine surviving out of a standard quantity supplied, and the bromine absorbed, are each expressed in c.c. of 0·01133N-thiosulphate per 5 c.c. sample.)

[NaOEt].	[SMe_2EtI].	% Reaction.	Br_2 present.	Br_2 used.	% C_2H_4.
21·03	11·34	0·0	21·20	—	—
17·31	7·62	32·8	18·90	2·30	15·3
13·11	3·42	69·8	16·53	4·67	14·7
9·69	—	100·0	14·60	6·60	14·4

(The mean of the figures in the last column, 14·8%, is entered, as the main result of this experiment, in Table I.)

TABLE V.

Illustrating the normal method of determining olefin proportion : ethylene from dimethylethylsulphonium iodide by the aspiration method.

(Solvent : EtOH. Temp. 63·95°. Initially [SMe_2EtI] = 0·0511M and [NaOEt] = 0·0977N. In the Table the alkali is expressed in c.c. of 0·02134N-acid per 5 c.c. sample, whilst the olefin is given by the amount of bromine, measured in c.c. of 0·01228N-thiosulphate, which survives, out of a standard amount supplied, in a 10 c.c. sample of the reaction mixture.)

Initial readings.		Final readings.	
Alkali.	Bromine.	Alkali.	Bromine.
22·78	25·30	10·90	13·43, 11·98, 11·50
22·84	25·20	10·86	12·47, 12·02
22·81 (mean)	25·25 (mean)	10·88 (mean)	12·28 (mean)

(Alkali consumed : 11·93 c.c. Olefin formed : 12·97 c.c. Proportion of olefin = 15·6%.)

TABLE VI.

Some additional second-order rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*), *and percentages of formed olefin, for the reaction of dimethylethylsulphonium iodide with sodium ethoxide* (*cf. Part VIII*).

(Solvent: EtOH. Temp. 45·08°.)

Initial concentrations.			
[SMe_2EtI].	[NaOEt].	10^5k_2.	% Olefin.
0·0207	0·0951	41·9	—
0·0213	0·0945	41·3	—
0·0208	0·0938	—	12·0
0·0213	0·0963	—	11·9

Estimation of Sulphides formed from Dimethyl-2-phenylethylsulphonium Ethoxide.—The apparatus usually employed for the estimation of ethylene or propylene by aspiration was used with slight modifications for the estimation of dimethyl sulphide in the product of the completed reaction between dimethyl-2-phenylethylsulphonium iodide and sodium ethoxide in ethyl alcohol at 64°. The conditions of reaction were the same as those under which the production of styrene was estimated. The usual bromine traps were omitted from the aspiration apparatus, and three traps containing saturated aqueous mercuric chloride were provided. The formed dimethyl sulphide was aspirated into these from the reaction mixture at 40° in a stream of nitrogen. The precipitated complex was collected and weighed. The assumption was made that it has the composition $3HgCl_2,2(CH_3)_2S$ (Phillips, *J. Amer. Chem. Soc.*, 1901, **23**, 253; Hughes and Ingold, *J.*, 1933, 1571; MacNulty, Thesis, London, 1938). The residual reaction mixtures from a number of such aspirations were combined, and worked up for methyl 2-phenylethyl sulphide. They were shaken with aqueous mercuric chloride, and the precipitated complex, assumed to have the composition $3HgCl_2,2C_6H_5{\cdot}S{\cdot}CH_3$, was collected and weighed. The result of these analyses have already been given (p. 2074).

SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Received, January 15th*, 1948.]

---

423. *Mechanism of Elimination Reactions. Part XIII. Kinetics of Olefin Elimination from* iso*Propyl-*, sec.*-Butyl-, and* 1*-Phenylethyldimethylsulphonium Salts in Alkaline Alcoholic Media.*

By E. D. HUGHES, C. K. INGOLD, G. A. MAW, and L. I. WOOLF.

Data are recorded to show the effects of certain structural changes on the rates of the substitutions and eliminations which secondary alkyldimethylsulphonium ions undergo in bimolecular reactions with ethoxide ions in anhydrous ethyl alcohol as solvent. Elimination rates are analysed, where possible, in terms of the separate rates of establishment of the double bond in the different branches of the secondary alkyl groups. The structural effects studied relate to those of α-linked methyl, ethyl, and phenyl substituents, and to the effect of a β-linked methyl substituent on the rate of establishment of a double bond between C_α and C_β.

The substitutions are composite, since either methyl or the secondary alkyl group may be displaced from the sulphonium ion in bimolecular substitution. In the case of the dimethyl-1-phenylethylsulphonium ion, which shows an outstandingly large rate of total bimolecular substitution, it is shown that this effect of the phenyl substituent is due mainly to an increased rate of displacement of the 1-phenylethyl group itself, rather than to any effect of this phenylated group on the rate of displacement of methyl. The effect of the phenyl substituent is regarded as essentially polar.

In the bimolecular elimination of the *sec.*-butylsulphonium ion, the double bond mainly enters the shorter alkyl branch, in contrast to the corresponding reaction of *sec.*-butyl bromide. The effect of an α-methyl or α-ethyl substituent is to increase the rate of establishment of a double bond between C_α and C_β, the effect of an α-phenyl substituent is to increase it strongly, and the effect of a β-methyl substituent is to decrease it, in contrast to what is observed with alkyl bromides. The interpretation of the results is considered in Part XVI.

IN the preceding paper a kinetic study was described the object of which was to establish the effect of structural changes in primary alkyl groups on the rates of the simultaneous substitutions and eliminations which arise in the decompositions of alkylsulphonium ions. The present paper describes a similar study of secondary alkyl groups combined in sulphonium ions.

Although, as compared with primary alkylsulphonium ions, secondary alkylsulphonium ions show an increased tendency to undergo unimolecular decompositions, these reactions are still difficult to realise in a mechanistically pure form. Therefore we again concentrated attention on the bimolecular reaction of substitution and elimination, which the simpler secondary, like the primary, alkylsulphonium ions undergo in the presence of a strongly nucleophilic reagent

and in an appropriate solvent. We have, in fact, kinetically analysed the reactions between secondary alkyldimethylsulphonium ions (*sec.*-Alk$\overset{+}{S}$Me$_2$) and ethoxide ions, in dry ethyl alcohol as solvent, the conditions being generally similar to those used in already described investigations on primary alkyldimethylsulphonium ions.

The alkyl groups now examined in combination as dimethylsulphonium ions are *iso*propyl, *sec.*-butyl, and 1-phenylethyl, which may be regarded as derived from ethyl by introduction of the substituents α-Me, α-Et and α-Ph, respectively. A comparison of the behaviour of *iso*propyl and *sec.*-butyl will show the effect of introducing the substituent β-Me in the secondary alkyl series.

With all these sulphonium ions under the conditions indicated, unimolecular reactions proceed at rates which are negligible in comparison with the rates of the bimolecular processes. The total reaction is thus experimentally of the second order, consisting partly of bimolecular substitution (S_N2) and partly of bimolecular olefin-elimination ($E2$), and the proportion in which olefin is produced remains constant during the change. Our procedure has been, as before, to measure the total rate constant, k_2, and then split it into its components, $k(S_N2)$ and $k(E2)$, on the basis of measurements of the olefin proportion.

In all cases the substitution can consist of two simultaneous substitutions, since either a methyl group, or the secondary alkyl group, may separate from the sulphonium sulphur atom and combine with the attacking ethoxide ion, forming methyl ethyl ether, or a secondary alkyl ethyl ether. However, in our work these two substitutions have been measured together.

$$\textit{sec.}\text{-Alk}\overset{+}{S}\text{Me}_2 + \bar{O}\text{Et} \longrightarrow \begin{cases} \text{MeOEt} + \textit{sec.}\text{-AlkSMe} \\ \textit{sec.}\text{-AlkOEt} + \text{SMe}_2 \end{cases} \quad (S_N2)$$
$$\text{HO·Et} + \text{olefin} + \text{SMe}_2 \quad (E2)$$

In the case of the *sec.*-butyl compound the elimination may consist of two simultaneous eliminations, since the olefinic double bond can be formed along either the shorter or the longer branches of the *sec.*-butyl group. These eliminations were in the first instance measured together; but it was important for our purpose to determine the rates of the separate processes, as given by the composition of the mixture of isomeric olefins formed in the reaction, because such figures must disclose the orientation laws for bimolecular olefin elimination in sulphonium salts, and must therefore help us to understand the rate relations.

The mixture of isomeric olefins formed in the decomposition of the *sec.*-butyl-sulphonium salt may contain but-1-ene and the *cis*- and *trans*-forms of but-2-ene. Two methods of analysis have been employed, following the pioneer work of Lucas, Dillon, and Young (*J. Amer. Chem. Soc.*, 1930, **52**, 1949, 1953), who attacked the same problem in the example of butenes formed in the alkaline alcoholysis of *sec.*-butyl bromide. They recommended converting the butenes into their dibromides. They found that the boiling points of 1 : 2-, *meso*-2 : 3-, and racemic 2 : 3-dibromo-*n*-butane were too close together to allow an easy separation by distillation. They also found that the other physical constants which they measured were symbatic with the boiling points, so that it was undesirable to make the measurement of two such physical properties of the ternary mixture of bromides the basis of analysis. What was done was to employ one physical property, *viz.*, the density at 25°, and one chemical property, which had been found to be non-symbatic with the physical properties. This was the second-order rate-constant for the reaction with potassium iodide in methyl alcohol at 75°. We first used this method, employing pure synthetic but-1-ene in order to control the isolation of the analytical sample, and to correct for the effect of any slight differences of solvent, temperature, or other conditions between Lucas, Dillon, and Young's kinetic determinations and ours. Our second method consisted of a quantitative distillation of the butenes themselves, with the aid of a special column, which Dr. I. Dostrovsky had built, and which he helped us to apply in these analyses. The results obtained by both methods are given in the following scheme:

$$\begin{matrix} \text{CH}_3\text{·CH}_2 \\ \text{CH}_3 \end{matrix}\!\!>\!\text{CH·}\overset{+}{S}\text{Me}_2 \xrightarrow[(E2)]{\bar{O}\text{Et}} \begin{matrix} \text{CH}_3\text{·CH} \\ \text{CH}_3 \end{matrix}\!\!>\!\text{CH} \begin{pmatrix} 26\%\,^1 \\ 27\%\,^2 \end{pmatrix} + \begin{matrix} \text{CH}_3\text{·CH}_2 \\ \text{CH}_2 \end{matrix}\!\!>\!\text{CH} \begin{pmatrix} 74\%\,^1 \\ 73\%\,^2 \end{pmatrix}$$

[1] By kinetic and physical analysis of the dibromides.
[2] By quantitative distillation of the hydrocarbons.

The but-2-ene appeared to consist mainly of the *trans*-isomeride. The two methods of analysis agree in giving the result that most of the elimination which takes place in the alkaline decomposition of the dimethyl-*sec.*-butylsulphonium ion occurs along the shorter branch of the *sec.*-butyl chain. This is a striking contrast to Lucas, Dillon, and Young's results for the

corresponding reactions of *sec.*-butyl bromide; and, accordingly, the opportunity of employing a modern column was taken to repeat their work. The outcome, as is mentioned in Part X (this vol., p. 2060), was that their findings were closely confirmed.

The results of the main series of measurements of the overall bimolecular rate-constants, and of the proportions in which olefins are formed in these reactions of the secondary alkyl-dimethylsulphonium ions, are assembled in Table I. In Table II these data are analysed in terms of the individual rate-constants for the total bimolecular reactions of substitution and the total bimolecular reactions of elimination. The substitution rate-constants are not further subdivided, but the elimination rate-constants are analysed in the last column of Table II into the rate-constants for elimination along the separate branches of the alkyl chain.

We shall comment first on the substitution rates. In the units employed in Table II, the substitution rate for the dimethylethylsulphonium ion, $CH_3 \cdot CH_2 \cdot \overset{+}{S}Me_2$, is given by $10^5 k_2 = 395$ (preceding paper). Now it follows indirectly from the work of Ingold and Kuriyan on the aqueous alkaline decomposition of this ion (*J.*, 1933, 991) that the substitution in alcoholic alkali will in this case proceed largely in the direction which involves the combination of one of the methyl groups with the attacking ethoxide ion to form methyl ethyl ether, but also to a

TABLE I.

Second-order rate constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*) *of, and percentages of olefin formed in, the reactions of secondary alkyl-dimethylsulphonium iodides and sodium ethoxide in dry ethyl alcohol at* 63·94°.

(Initially [$AlkSMe_2I$] ~0·05 and [NaOEt] ~0·095.)

Alk. in $(Alk\overset{+}{S}Me_2)\bar{I}$.	$10^5 k_2$.		% Olefin.	
	Individual values.	Mean.	Individual values.	Mean.
*iso*Propyl	1590, 1590, 1550	1580	65·8, 65·7, 65·6	65·7
sec.-Butyl	1200, 1210	1205	57·8, 57·6	57·7
1-Phenylethyl	—	9770 *	58·8, 58·4, 59·0, 60·4	59·1

* Extrapolated from the following results at lower temperatures, *viz.*,

$10^5 k_2$ = 27·4, 27·6 (mean 27·5) at 19·98° (T = 293·13°)
" = 962, 960 (mean 961) " 45·08° (T = 318·23°)

by means of the derived equation

$$\log_{10} k_2 = 16{\cdot}00 - 26{,}230/(2{\cdot}303 \times 1{\cdot}986 \times T).$$

TABLE II.

Analysis of kinetic data for the reactions of alkyl-dimethylsulphonium iodides with sodium ethoxide in ethyl alcohol at 64°, *showing the variation of the rates of bimolecular substitution and elimination with changes in the structure of the alkyl group.*

Sulphonium ion.	$10^5 k_2$.	% Olefin.	$10^5 k(S2)$.	$10^5 k(E2)$. Total.	$10^5 k(E2)$. Each branch.
$CH_3 \cdot CH(CH_3) \cdot \overset{+}{S}Me_2$	1580	65·7	540	1040	520, 520
$CH_3 \cdot CH_2 \cdot CH(CH_3) \cdot \overset{+}{S}Me_2$	1205	57·7	510	695	185, 510
$C_6H_5 \cdot CH(CH_3) \cdot \overset{+}{S}Me_2$	9770	59·1	4000	5775	—, 5775

significant degree in the direction in which the ethyl group is similarly displaced to form diethyl ether. No doubt the substitutions of the secondary alkyl-dimethylsulphonium ions will pursue two directions also, each of the observed substitution rates being, therefore, the sum of two components, one relating to the formation of a secondary alkyl ethyl ether and the other to the formation of methyl ethyl ether. Both these component rates are likely to be changed on passing from one alkyldimethylsulphonium ion to another, the former because of polar and

steric effects on the tendency of the alkyl group itself to be displaced by substitution, and the latter through an " orienting " effect of the secondary alkyl group on the rate of displacement of methyl. As yet we have no systematic data which enable these effects in general to be distinguished; but in the most extreme case, that of the dimethyl-1-phenylethylsulphonium ion, the total rate of substitution of which is much larger than that of any of the purely aliphatic sulphonium ions, we know that most of the rate is due to the relatively facile displacement of the 1-phenylethyl group to form ethyl 1-phenylethyl ether. It has in fact been directly confirmed in preparative experiments involving the decomposition of dimethyl-1-phenylethylsulphonium ions by ethoxide ions in ethyl alcohol, that such of the 1-phenylethyl radical as does not appear in the form of styrene can be recovered in high yield as ethyl 1-phenylethyl ether.* This effect is regarded as essentially polar.

Finally we direct attention to the following facts concerning the elimination rates. In contrast to bimolecular elimination in *iso*propyl and *sec.*-butyl bromides, for which the higher homologue has the larger rate (cf. Part X), the rate of bimolecular elimination drops from the dimethyl*iso*propyl- to the dimethyl-*sec.*-butyl-sulphonium ion. The fall of rate is due entirely to the slower establishment of the double bond in that alkyl branch which becomes lengthened in the *sec.*-butyl group, the rate of its entrance into the alkyl branches which remain similar in the two conpounds being only very slightly reduced. On the other hand, the rate of entrance of the double bond into the corresponding alkyl branch of the 1-phenylethyl group is very much increased, the 1-phenyl substituent of this sulphonium ion, unlike the 2-methyl substituent of the *sec.*-butyl-sulphonium ion, having a strong effect on the reaction of that alkyl branch to which it does not itself belong, *i.e.*, a strong " orienting " action. 1-Methyl and 1-ethyl substituents have a similar, but weaker, action, as may be seen by comparing the elimination rates for the *iso*propyl- and *sec.*-butyl-sulphonium ions with that of the ethyl-sulphonium ion (preceding paper). The theory of these relationships will be discussed in Part XVI.

Experimental.

Materials.—The required sulphonium iodides were all prepared from the secondary alkylthiols, by way of the secondary alkyl methyl sulphides, to which methyl iodide was added in nitromethane as solvent (cf. preceding paper). The 2-propyl and 2-*n*-butyl salts were purified by repeated precipitation at low temperatures from solution in anhydrous ethyl alcohol by addition of dry ether. The 1-phenylethyl salt readily became converted into an oil in the presence of solvents other than ether, and only went solid again when such solvents were removed by pumping. It was therefore purified by washing it with ether after it had largely solidified. The iodine contents of the salts were determined as a check on their purity: dimethyl*iso*propylsulphonium iodide gave I = 54·67% (Calc., 54·69%); dimethyl-*sec.*-butylsulphonium iodide gave I = 51·60% (Calc., 51·58%); and dimethyl-1-phenylethylsulphonium iodide gave I = 43·17% (Calc., 43·17%).

The ethyl alcohol employed in the kinetic measurements was prepared by drying commercial " absolute " ethyl alcohol by the method of Smith and Manske (preceding paper).

Methods for Measurements of Rates and Olefin Proportions.—The methods were the same as those given in the preceding paper. The special method there described for the preparation of solutions of dimethyl-2-phenylethylsulphonium iodide was not required for its more soluble isomeride, the 1-phenyl compound.

Results of Measurements of Rates and Olefin Proportions.—The results of the main series of measurements are summarised in Table I. In illustration of the experimental basis of these figures, we give in Table III the record of the first of the three rate measurements made at 63·94° on dimethyl*iso*propylsulphonium iodide, and in Table IV the third of the three olefin determinations made for this temperature on the same substance.

Table III.

Illustrating determinations of total second-order rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*) *: Dimethyliso**propylsulphonium iodide** (Expt. A).*

(Solvent: EtOH. Temp. 63·94°. Initially [SMe_2PrI] = 0·0537M and [NaOEt] = 0·0981N. In the Table [SMePrI] and [NaOEt] are each expressed in c.c. of 0·02145N-acid per 5 c.c. sample.)

t (min.).	[NaOEt].	[SMe_2PrI].	$10^3 k_2$.	*t* (min.).	[NaOEt].	[SMe_2PrI].	$10^3 k_2$.
0	22·77	12·47	—	6	18·15	7·85	14·7
1	21·82	11·52	(13·7)	7	17·71	7·41	14·4
2	20·85	10·55	14·8	8	17·22	6·92	14·5
3	20·03	9·73	15·0	10	16·25	5·95	15·0
4	19·24	8·94	15·4	12	15·65	5·35	14·7
5	18·79	8·49	14·4	∞	10·30	—	—

(Mean $k_2 = 14·8 \times 10^{-3}$ sec.$^{-1}$ g.-mol.$^{-1}$ l.; corrected for solvent expansion, $k_2 = 15·9 \times 10^{-3}$ sec.$^{-1}$ g.-mol.$^{-1}$ l.)

* These experiments were carried out by Dr. S. H. Harvey. They were primarily directed to the solution of a problem relating to the Walden inversion, and will be published shortly in association with other work in that field.

The reaction with dimethyl-1-phenylethylsulphonium iodide went too rapidly at 63·94° to allow an accurate rate measurement. However, the proportion of olefin in the product of the completed reaction at this temperature was measured. The rate itself was obtained by extrapolation from rate measurements made at lower temperatures, as particularised in the footnote under Table I.

A few further measurements are recorded for convenience in Table V, although they are more relevant to Part VIII than to this paper (cf. this vol., p. 2049).

TABLE IV.

*Illustrating determinations of the proportion of formed olefin : propylene from dimethyl-iso**propylsulphonium iodide by the aspiration method (Expt. C).*

(Solvent : EtOH. Temp. 63·94°. Initially [SMe_2PrI] = 0·0507M and [NaOEt] = 0·0961N. In the Table the alkali is expressed in c.c. of 0·02125N-acid per 5 c.c. sample, whilst the olefin is given by the amount of bromine, measured in c.c. of 0·02925N-thiosulphate, which survives, out of a standard amount supplied, in a 10 c.c. sample of the reaction mixture.)

Initial readings.		Final readings.	
Alkali.	Bromine.	Alkali.	Bromine.
22·53	54·60	10·65	31·80, 32·65, 31·71
22·53	54·68	10·67	31·73, 31·84
22·53 (mean)	54·64 (mean)	10·66 (mean)	31·89 (mean)

(Alkali consumed : 11·87 c.c. Olefin formed : 22·75 c.c. Proportion of olefin = 65·6%.)

TABLE V.

Additional second-order rate-constant (k_2 in sec.$^{-1}$ g.-mol.$^{-1}$ l.) and percentage of formed olefin for the reaction of dimethylisopropylsulphonium iodide with sodium ethoxide (cf. Part VIII).

(Solvent : EtOH. Temp. 45·08°.)

Initial concentrations.			
[SMe_2PrI].	[NaOEt].	10^5k_2.	% Olefin.
0·0201	0·0966	187	—
0·0207	0·0968	—	60·6 [1]

[1] Mean of six measurements ranging from 60·4 to 60·9%.

Experiments with But-1-ene and its Dibromide.—The hydrocarbon was prepared, as described by Lucas and Dillon (*J. Amer. Chem. Soc.*, 1928, **50**, 1460), by allowing allyl bromide to interact with methylmagnesium iodide, from which the ether used in its preparation had been largely removed by distillation. The gas evolved at about 75° was washed with 30% aqueous methyl alcohol and 37% perchloric acid, and dried with calcium chloride. Part of this material was used for the preparation of 1 : 2-dibromo-*n*-butane, as follows.

An all-glass apparatus was employed. The bromine was contained in a warmed glass bulb, and was carried as vapour in a stream of nitrogen through a capillary tube to the bottom of a second bulb, which contained the hydrocarbon and was cooled in a bath of ice and salt. The object of the arrangement was to secure good stirring where the bromine enters, and thus to avoid local excess of the halogen. The upper part of the bulb was fitted, by means of a ground joint, with a reflux condenser, consisting of a spiral tube sealed through the bottom of a container filled with ether and solid carbon dioxide. As soon as a permanent yellow colour appeared in the brominated hydrocarbon, this was washed successively with acidified sodium sulphite, sodium hydrogen carbonate, and water. It was then dried with calcium chloride and distilled at 50 mm. (barostat), with high reflux-ratio, through a " 15-plate " adiabatic column of glass helices. The boiling point (80·2—80·3/49·8 mm.) and physical constants agreed practically exactly with those given by Lucas, Dillon, and Young (*loc. cit.*).

This material was used in order to correlate the conditions of our kinetic analysis with those used by Lucas, Dillon, and Young. The chief conditions to which the rate-constants are sensitive are solvent-composition, temperature, and ionic strength. The object of the correlation was to enable us to use Lucas, Dillon, and Young's rate-constants for the dibromides of all the three butenes, by applying to the recorded figures a small percentage correction in order to bring them into correspondence with our slightly different solvent, temperature and ionic strength. The reaction studied was the interaction between the butene dibromides and potassium iodide in " 99% " methyl alcohol at 75°. A large batch of solvent was made up by the addition of the requisite amount of water to dry methyl alcohol : this material was used for all the rate measurements. Our thermostat ran at 74·98° ± 0·02°. After some preliminary trials, we settled to a standard procedure in which the initial concentration of potassium iodide was 0·27M and the initial concentration of dibromide was 0·064M. Under these conditions the second-order rate law was accurately obeyed, and the reaction with 1 : 2-dibromo-*n*-butane had the rate-constant 0·0800 min.$^{-1}$ g.-mol.$^{-1}$ l. For this substance, Lucas, Dillon, and Young record the rate-constant 0·0765 min.$^{-1}$ g.-mol.$^{-1}$ l., and hence it appears that 4·6% must be added to each of their rate-constants in order to obtain figures applying to our kinetic conditions.

Other portions of the synthetic sample of but-1-ene were employed in order to establish a process for the recovery of butenes from mixtures such as would arise by the decomposition of dimethyl-*sec.*-butylsulphonium ethoxide. In particular it was shown that but-1-ene, when recovered from a mixture

containing ethyl alcohol and dimethyl sulphide by a process corresponding to that described below, gave a dibromide having properties identical with those of the above standard sample of dibromide.

*Analysis of the Butenes derived from Dimethyl-*sec.*-butylsulphonium Ethoxide (First Method).*—Dry ethyl alcoholic solutions of dimethyl-*sec.*-butylsulphonium iodide and of sodium ethoxide were mixed at 50° to give 2 l. of a solution 0·33M with respect to the sulphonium iodide and 0·66M with respect to sodium ethoxide. The temperature was raised to 70° during several hours, after which water at 70° was run in. There was a brisk evolution of gas, which passed through an ordinary reflux condenser, and was then condensed in a trap cooled in liquid air. The temperature of the reaction mixture was raised until the solvent boiled, and air was then passed through it in order to carry all the butenes into the cooled trap. The trap was warmed to −80°, and its contents were then added to a solution of mercuric chloride (15 g.) in ethyl acetate (62 g.) at −17°. The mixture, in which a heavy white precipitate had formed, was kept at this temperature overnight, and then distilled through a special column arranged for use at low temperatures.

This was a " 5-plate " column of Vigreux type, 80 cm. long and 7 mm. internal diameter, with low hold-up. Its purpose was to separate the butenes from other substances without separating the isomeric hydrocarbons from one another. It was lagged with 2 cm. of cotton wool surrounded by a double-walled jacket through which ice-cold water was pumped during distillation. It was connected by means of ground joints to the distillation vessel below, and, through a drip-indicator, to the first of two condensers above. The drip-indicator was observed through thick " Perspex " windows inserted into the lagging. The cooling jacket of the first condenser had three tubulures, two near the bottom and one at the top, so that its effective height could be altered to give any desired reflux ratio, including total reflux. The method was to pass the cooling fluid into, and out from, the bottom two tubulures, and keep the top one closed, after the height of the cooling liquid in the jacket had been adjusted by withdrawing from it, or letting in through it, the right amount of air. The top of this condenser was connected by a ground joint to the second condenser, which was designed to give total condensation, and which delivered, through another lagged drip-indicator, into a tube leading nearly to the bottom of a collecting flask, cooled with ether and solid carbon dioxide. The second condenser was also connected by way of a ground joint to a trap, and thence to a calcium chloride tube, both cooled with solid carbon dioxide. The cooling fluid for both condensers was dry ether at −80°. It was syphoned from a Dewar vessel, through a coil immersed in a mixture of chloroform, carbon tetrachloride, and solid carbon dioxide; and, having passed through either condenser jacket, it was collected in another Dewar vessel, which was substituted for the source vessel as necessary. The runs of tubing were lagged, except for short rubber sections possessing screw clips for regulating the rate of flow.

A eutectic alloy of sodium and potassium was made up in a flask having a ground joint which fitted the first condenser described above. The alloy was cooled to −80°, and the hydrocarbon distillate was added. The condenser was fitted, and the flask was allowed to warm until the butenes were boiling under total reflux. No hydrocarbon appeared in a CO_2-cooled trap attached to the top of the condenser, and there was very little discoloration of the alloy. After some hours the butenes were transferred by distillation through an all-glass connecting tube to the bromination apparatus, and brominated, exactly as described above for synthetic but-1-ene. The brominated butenes were washed and dried as described for 1 : 2-dibromo-*n*-butane, and then submitted to the following distillations, designed to remove any low-boiling, and also any high-boiling, non-isomeric impurities.

First, the mixture was put under the " 15-plate " column, and boiled with total reflux at 50 mm. pressure (barostat) until thermal equilibrium had been established. Then, very slowly, four drops were taken off as distillate. The temperature at the time of the fourth drop was 73·7°/50 mm. The distillation was then stopped, and the column allowed one hour to drain. The liquid in the distilling flask was then poured through it, and it was again allowed to drain. The four drops withdrawn as distillate would be insufficient appreciably to affect the proportions of the isomeric dibromides, but they could have removed an amount of non-isomeric impurity which would have been enough to upset the analysis. The second distillation process consisted of transferring the bromides by non-ebullient distillation at 50 mm., under conditions of negligible hold-up, from the distilling flask, which was finally heated on a boiling water-bath, to a receiving flask, which was cooled in ice and salt. The short ground-jointed connecting tube led nearly to the bottom of the cooled receiving flask, which was the only condenser. Its efficiency as a condenser was shown by the fact that no condensate collected in the CO_2-cooled trap, to which also it was connected. At this stage the density of the bromides was $d_4^{25°}$ 1·78257. They were then again submitted to above-described distillations, first under the " 15-plate " column, and then from flask to flask. In the distillation under the column, three drops were taken off, the temperature at the time of the third being 78·5°/50 mm., and then three more drops were withdrawn, the temperature at the time of the sixth being still 78·5°/50 mm. It thus appeared that volatile non-isomeric impurities had been fully removed; and even the withdrawal of six drops could not seriously have affected the compositions of the isomeric dibromobutanes. After the non-ebullient distillation, the density was $d_4^{25°}$ 1·78262. This was accepted as the correct value. Densities were measured with a 1 c.c. pyknometer and a microbalance, the technique being generally similar to that developed in these laboratories for work involving heavy hydrogen water or heavy oxygen water (cf., *e.g.*, *J.*, 1934, 498, 1593). The accuracy was about 3 in 10^6, *i.e.*, rather greater than corresponds to the number of figures we quote.

Two measurements were made, using this sample, of the rate-constant of the reaction with potassium iodide in " 99% " methyl alcohol at 74·98°, the conditions being as closely as possible identical with those employed in the experiments with synthetic 1 : 2-dibromo-*n*-butane. The results were as follows:

Initial concentrations.		k_2
[KI].	[$C_4H_8Br_2$].	(min.$^{-1}$ g.-mol.$^{-1}$ l.).
0·2661	0·06366	0·0755
0·2705	0·06385	0·0759

The mean of these rate-constants, in combination with density, gives the analytical composition already quoted.

*Analysis of the Butenes derived from Dimethyl-*sec.*-butylsulphonium Ethoxide (Second Method).*—The butene mixture was also analysed by the method of quantitative distillation. In this case twice the formerly used quantities of dimethyl-*sec.*-butylsulphonium iodide and sodium ethoxide were employed, the butenes being collected, and freed from sulphides by treatment with mercuric chloride in ethyl acetate, as before. On this occasion particular care was taken to remove the last trace of butenes from the solvent, which was used as a " chaser " in order to clear the butenes from the column at the end of the distillation. This meant that a quantity of the order of one drop of ethyl acetate became collected with the butenes, and that therefore the sodium–potassium alloy with which they were next treated became considerably tarnished. However, the treatment was continued with fresh portions of alloy until tarnishing no longer occurred. The butenes were then mixed with a little pure pentane (to act as a " chaser ") and distilled in the apparatus described below, the building and operation of which were supervised by Dr. I. Dostrovsky.

The bottom of the distillation bulb contained a thimble-shaped well through which a coil of fine platinum wire was sealed. Through this wire a controlled supply of heat could be introduced by the passage of an electric current. Adventitious heat-exchange was prevented by inserting the bulb, and its connexion to the column, into a Dewar vessel. The column, packed with small glass helices, was enclosed throughout its length with a silvered vacuum jacket, which was connected with a backed diffusion pump. At the head of the column was placed a thermometer, having its bulb in contact with the top of the packing. Above the thermometer, and surrounding its stem, was a reflux condenser, capable of condensing all the vapour that entered it. The top of the condenser was sealed. Between the bottom of the condenser and the top of the packing, a distance of about 2 cm., a narrow, upward-sloping side-tube was inserted, through which butene vapour, but not liquid, could be withdrawn. This tube led first to a wide U-tube, containing mercury through which gas could be bubbled by a small pressure difference, and thence, by a 3-way stopcock, to either of two large aspirators.

In preparation for a distillation, the column jacket was pumped to a hard vacuum, the condenser circuit was started and regulated, and the aspirators were filled. The cooling liquid for the condenser was dry ether which was drawn from a reservoir by means of a circulating pump, forced through a coil immersed in a mixture of chloroform, carbon tetrachloride, and solid carbon dioxide, and thence, by lagged tubes, through the condenser jacket, and back into the reservoir. Thermometers were provided for the measurement of the temperature of the ether as it entered and left the condenser jacket. These temperatures were regulated to be close to −25°, because this temperature gave adequate condensing power, and it had been found that a lower temperature over-cooled the refluxing butenes, so that the temperature at the head of the column fell below the boiling point. The aspirators were supplied with water made alkaline with potassium carbonate. The purpose of the alkali was to suppress any tendency for interaction between the butenes and the water. Losses due to the solubility of butenes in water were reduced by using the same liquid on each occasion.

The butene mixture, which had in the meantime been kept in the distilling bulb at −80°, was now heated by a current given by a 6-volt battery and controlled by a rheostat. Air was at first driven out through the mercury by the ascending vapour: the air was allowed to escape by way of a side-tube. Soon after the butenes had reached the head of the column, and had begun to condense, all passage of gas through the mercury ceased. The refluxing was allowed to continue for a further period in order to ensure thermal equilibrium in the column. Then the butene vapour was withdrawn by running water slowly out of the aspirators, and a series of readings was taken of the temperature at the head of the column and, simultaneously, of the volume of gas collected. A water manometer had been provided so that the pressure of the gas could be read, and its temperature was taken to be that of the emerging water: this was measured, thus permitting correction of the volumes to normal temperature and pressure. The whole of the butenes were eventually collected in the aspirators. When the pentane reached the top of the column the temperature rose sharply and the distillation was stopped.

The quantitative result has already been given. The effect of the distillation was to strip the but-1-ene (b. p. −6°) from the total but-2-enes (b. p. 2—3°) quite sharply. By turning the 3-way tap the isomerides could be collected in separate aspirators. The but-2-ene fraction appeared to consist mainly of the *trans*-isomeride, but the column could not have separated the stereoisomerides sharply, even if both had been present in substantial quantities.

(This method was also used for the analysis of the butenes evolved when *sec.*-butyl bromide is treated with ethyl-alcoholic potassium hydroxide. The result, which confirms an earlier analysis by Lucas, Dillon, and Young, has already been mentioned in Part X.)

SIR WILLIAM RAMSAY and RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Received, January 15th,* 1948.]

424. *Mechanism of Elimination Reactions. Part XIV. Kinetics of Olefin Elimination from* tert.*-Butyl- and* tert.*-Amyl-dimethylsulphonium Salts in Alkaline and Acidic Alcoholic Media.*

By E. D. Hughes, C. K. Ingold, and L. I. Woolf.

Data are recorded to show the effect of homology on the rates of the constituent substitutions and eliminations which tertiary alkyl-dimethylsulphonium ions undergo in bimolecular reactions with ethoxide ions, and also in unimolecular reactions, in ethyl alcohol as solvent. It was readily possible to isolate each of these kinetic types of reaction. Dimethyl-*tert.*-butyl- and -*tert.*-amylsulphonium ions were studied, and the amylenes produced from the latter by each reaction mechanism were analysed, in order to permit a division of the elimination rates and proportions into those parts which apply to the establishment of the double bond along the separate branches of the tertiary alkyl groups.

The bimolecular eliminations of these ions in ethyl-alcoholic sodium ethoxide proceed considerably more rapidly than do the corresponding reactions of the simpler secondary alkyl, and much more rapidly than do those of the primary alkyl, dimethylsulphonium ions; and their speed is too great to permit the measurement of anything more than limits to the rates of the accompanying bimolecular substitutions. Bimolecular elimination proceeds less rapidly in the *tert.*-amyl than in the *tert.*-butyl group, and this is the total result of a large fall of rate for the establishment of the double bond in the alkyl branch which becomes lengthened, together with quite small decreases of rate for the entrance of the double bond into the alkyl branches which remain similar in the two homologues. In bimolecular elimination from the amylsulphonium ion the double bond enters mainly into the shorter branches of the tertiary alkyl group. These results contrast strikingly with those applying to bimolecular elimination from *tert.*-butyl and *tert.*-amyl bromides: they are discussed theoretically in Part XVI.

The rate of the overall unimolecular reaction is considerably greater for the *tert.*-amyl- than for the *tert.*-butyl-sulphonium ion. The rate of unimolecular substitution is increased, but the proportion of such substitution is decreased in the higher homologue. The rate, and the proportion, of elimination are increased in the amylsulphonium ion. The increase of elimination rate is due to a large increase in the rate of establishment of the double bond in the alkyl group which becomes lengthened, reinforced by smaller increases in the rate at which it enters the branches which remain similar in the two compounds. The increase in the proportion of elimination is the net result of a large increase in the proportion in which the double bond enters the lengthened alkyl branch, partly off-set by notable decreases in the proportions in which it enters the other alkyl branches. In unimolecular elimination from the *tert.*-amylsulphonium ion the double bond enters mainly into the long branch of the *tert.*-amyl group. These relations present marked contrasts to those shown by the bimolecular reactions of the sulphonium ions, but close similarities to those displayed by the unimolecular reactions of the analogous alkyl bromides. The theory of the matter is considered in Part XVI.

In this paper we are again concerned with the effects of structural modifications in an alkyl group on the kinetics of the substitutions and eliminations undergone by alkylsulphonium ions. The two preceding papers reported investigations on primary and secondary alkyl groups in alkyl-dimethylsulphonium ions; and the present paper records a corresponding study of tertiary alkyl groups in similar combination, *tert.*-$AlkSMe_2^+$.

The work on the primary and secondary alkyl-dimethylsulphonium ions was restricted to the bimolecular decompositions which they undergo in the presence of a strongly nucleophilic reagent; for the unimolecular reactions of these substances are for the most part difficult to isolate in a mechanistically pure form, even those of secondary alkylsulphonium ions. On the other hand, the tertiary alkyl-dimethylsulphonium ions, although they still exhibit bimolecular reactions, which can be made to become the exclusive modes of decomposition by operating with a moderate concentration of a strongly nucleophilic reagent, also display unambiguous unimolecular reactions, which it is equally easy to isolate by avoiding the presence in considerable concentration of strongly nucleophilic reagents. Accordingly the opportunity has been taken to investigate the kinetics of both modes of reaction of these tertiary alkylsulphonium ions, with the main object of disclosing the effect of structure on the unimolecular, as well as on the bimolecular, reactions of elimination. As before, the bimolecular reactions which have been studied are the reactions between the alkyl-dimethylsulphonium ions and ethoxide ions in ethyl alcohol: the unimolecular reactions are those which the tertiary alkyl-dimethylsulphonium ions undergo in ethyl-alcoholic solvents in the absence of large amounts of alkali.

It should be made clear that the reason why unimolecular elimination is so much more prominent in the reactions of tertiary alkylsulphonium salts than in those of the analogous primary and secondary alkyl compounds is not that bimolecular elimination from tertiary alkyl groups in sulphonium ions is attended with any greater difficulty than from primary or secondary alkyl groups in such ions. On the contrary, we can establish that the facility of

such bimolecular eliminations increases from primary to secondary, and from secondary to tertiary, alkyl groups: the increases are, indeed, considerable. The prominence of unimolecular elimination in the reactions of the tertiary alkyl compounds is due to the circumstance that the increasing facility of unimolecular reactions from primary to secondary, and from secondary to tertiary, alkyl groups is found, wherever demonstration is possible, to be an extremely steep function of structure. We should expect this, if the influence of the alkyl groups is largely polar; for unimolecular rates depend on a polar bond-fission, which must require the more internal electrical compensation, and therefore must act the more strongly on a polarisable group, as there is no electrically countervailing, contemporaneous bond-formation.

Table I is given to illustrate the increase in the rate of bimolecular olefin elimination (*E*2) along the alkyl series primary, secondary, tertiary, in the reactions of alkyl-dimethylsulphonium ions with ethoxide ions. The second-order rate-constants, $k(E2)$, refer to the formation of ethylene, propylene, and *iso*butylene from dimethyl-ethyl-, -*iso*propyl-, and -*tert.*-butyl-sulphonium iodide, respectively, by reaction with ethyl-alcoholic sodium ethoxide. One observes that each additional methyl branch in the variable alkyl group increases the rate of bimolecular elimination by, roughly, 25-fold.

TABLE I.

Second-order rate-constants, percentages of olefin formed, and separate rate-constants for bimolecular substitution, $k(S_N2)$, *and elimination,* $k(E2)$, *(sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.) in the reactions of primary, secondary, and tertiary alkyl-dimethylsulphonium ions with ethoxide ions in dry ethyl alcohol at* 45·08°.

(Initially $[AlkSMe_2I] \sim 0{\cdot}02$ and $[NaOEt] \sim 0{\cdot}095$.)

Alk in $(Alk\overset{+}{S}Me_2)\bar{I}$.	10^5k_2.	% Olefin.	$10^5k(S_N2)$.	$10^5k(E2)$.	Ref.
$CH_3{\cdot}CH_2{\cdot}$	41·6	12·0	36·6	5·0	Part XII
$(CH_3)_2CH{\cdot}$	187	61	73	114	,, XIII
$(CH_3)_3C{\cdot}$	2930	100	> 90 *	2930	,, VIII

* Based on an assumed maximum error in the olefin proportions of 3% for percentages in the neighbourhood of 100 (it is proportionately less for lower percentages—cf. Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 900).

The tertiary alkylsulphonium ions which have been comparatively examined are the dimethyl-*tert.*-butylsulphonium and the dimethyl-*tert.*-amylsulphonium ions. In the first instance, they have been studied with respect to their bimolecular reactions with ethoxide ions in ethyl alcohol. In the presence of some tenths molar sodium ethoxide, these bimolecular reactions take place without sensible amounts of accompanying unimolecular processes; it can be calculated that the latter constitute a proportion of the order of 0·1% of the total reaction of the dimethyl-*tert.*-butylsulphonium ion. Thus the bimolecular reactions of these tertiary alkyl-sulphonium ions can be isolated much more clearly than can the corresponding bimolecular reactions of the tertiary alkyl bromides (cf. Part XI).

The bimolecular reactions of the tertiary alkylsulphonium salts may be formulated as follows:

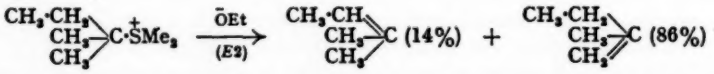
$$\textit{tert.}\text{-}Alk\overset{+}{S}Me_2 + \bar{O}Et \longrightarrow \begin{cases} MeOEt + \textit{tert.}\text{-}AlkSMe \\ \textit{tert.}\text{-}AlkOEt + SMe_2 \end{cases} \quad (S2)$$

$$HOEt + Olefin + SMe_2 \quad (E2)$$

There are thus two possible substitutions, but they are not accurately measurable, even together, in the presence of the much more rapid elimination. The total bimolecular rate, and the proportion of olefin formed, have, however, been measured. These data together provide the bimolecular elimination rate.

The elimination (*E*2) from the *tert.*-butylsulphonium ion is a single reaction, but the elimination from the *tert.*-amylsulphonium ion consists of two simultaneous processes; for the olefinic double bond can be formed along the longer branch, or along one of the two shorter branches of the *tert.*-amyl chain, to form trimethylethylene or 1-methyl-1-ethylethylene. It was important to determine the proportions of these products, since data for the orientation of any reaction capable of forming isomerides should be subject to the same theory as that by which the relative rates of the reaction in different compounds are interpreted. The

orientation ratio has therefore been determined by analysis of the formed amylenes, and on this basis the total bimolecular elimination rate has been split up into its components. Each of the amylenes has only a single stereoisomeric form, and hence the analysis could be simply performed by the measurement of a physical property: we used the refractive index. The results were as indicated:



These figures were obtained with the initial concentrations [SMe_2AlkI] ~ 0·09 and [NaOEt] ~ 0·25M, in " 97% " ethyl alcohol * at 24°, *i.e.*, in conditions similar as to ionic strength, solvent, and temperature to those which relate to the rate-constants, and proportions of total olefins, listed and compared below. However, the ratio in which the isomeric amylenes are formed seems to be relatively insensitive to concentration changes within the range of those concentrations which give nearly pure bimolecular kinetics. The greatest observed variation was with [$AlkSMe_2I$] ~ 0·15 and [NaOEt] ~ 2M, when the proportion of trimethylethylene fell to 10%. These proportions are widely different from those obtaining in the corresponding bimolecular reaction of *tert.*-amyl bromide (71% of trimethylethylene—cf. Part XI).

The principal data by means of which dimethyl-*tert.*-butyl- and -*tert.*-amyl-sulphonium salts may be compared with respect to rates of their total bimolecular reactions with ethyl-alcoholic sodium ethoxide, and with respect to the proportions in which total olefins are formed in these reactions, are assembled in Table II.

TABLE II.

Second-order rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*) *and percentage of olefin formed in bimolecular reactions of tertiary alkyl-dimethylsulphonium iodides with sodium ethoxide in " 97% " ethyl alcohol at* 24·0°.

Alk in $(AlkSMe_2)\bar{I}$.	Initial concentrations. [AlkSMe₂I].	Initial concentrations. [NaOEt].	10^5k_2.	% Olefin.
	0·047	0·256	79·7	—
	0·024	0·256	—	100
	0·032	0·461	71·2	—
	0·034	0·447	—	99
	0·091	0·234	58·1	—
	0·085	0·233	—	96
	0·091	0·430	50·9	—
	0·047	0·449	—	98

The results are divisible into two sets, those applying to initial alkali concentrations [NaOEt] ~ 0·25M, and those relating to the initial concentrations [NaOEt] ~ 0·45M. The rate-constants for each compound under these two conditions of concentration show that the reactions are subject to a negative salt effect. This is to be expected: the details of the phenomenon are being independently investigated. In the meantime it makes little difference which of the two common ionic strengths we choose for the purpose of comparing the results for the *tert.*-butyl-sulphonium salt with those for the *tert.*-amyl-salt. In Table III we make the comparison for the lower initial alkali concentration. One observes that the lower bimolecular elimination rate for the *tert.*-amyl compound than for the *tert.*-butyl compound is the total result of a large fall of rate for the establishment of the double bond along the alkyl branch which becomes lengthened in the *tert.*-amyl group, and of very small decreases of rate for the formation of the double bond in the branches which remain similar in the two homologues. The whole result forms a striking contrast to that which was obtained for the corresponding bimolecular reactions of *tert.*-butyl and *tert.*-amyl bromides. It was found that in this case the bimolecular elimination from the amyl group was faster, the increase being due entirely to the increased rate of establishment of the double bond along the alkyl branch which becomes lengthened in the *tert.*-amyl group (cf. Part XI). The theory of these relations will be discussed in Part XVI.

* The alcohol–water mixture thus designated was made up to contain 2·8% by weight of water.

TABLE III.

Analysis of kinetic data for the bimolecular reactions of tertiary alkyl-dimethylsulphonium iodides with sodium ethoxide (~ 0·25M) in " 97% " ethyl alcohol at 24°, showing the dependence of the bimolecular elimination rate on alkyl structure.

Alk in $(Alk\overset{+}{S}Me_2)\bar{I}$.	10^5k_2.	% Olefin.	$10^5k(E2)$. Total.	$10^5k(E2)$. Each branch.
tert.-Butyl.....	79·7	100	79·7	26·6 . . . CH_3 26·6 . . . CH_3>C· 26·6 . . . CH_3
tert.-Amyl.....	58·1	96	55·8	7·8 . . . $CH_3{\cdot}CH_2$ 24·0 . . . CH_3>C· 24·0 . . . CH_3

When the ethoxide ion concentration falls below 0·01M, the unimolecular reactions of dimethyl-*tert.*-butyl- and -*tert.*-amyl-sulphonium ions become important. By working in very dilute alkaline, or in neutral or acidic, solution, these reactions can be isolated, the bimolecular processes being practically completely suppressed. The simultaneous reactions which now take place may be represented as follows:

$$tert.\text{-}Alk\overset{+}{S}Me_2 \xrightarrow[\text{slow}]{} tert.\text{-}\overset{+}{A}lk + SMe_2 \xrightarrow[\text{fast}]{(EtOH)} \begin{cases} \overset{+}{H} + tert.\text{-AlkOEt} + SMe_2 & (S_N1) \\ \overset{+}{H} + \text{Olefin} + SMe_2 & (E1) \end{cases}$$

Here there can be no second substitution process leading to a *tert.*-alkyl methyl sulphide, as there can be in bimolecular substitution, because the rate of the unimolecular heterolysis of the methyl group from the sulphonium ion will be altogether too small. Another contrast to the bimolecular decomposition is that the represented reactions of unimolecular substitution and elimination proceed at quite comparable rates. For both dimethyl-*tert.*-butyl- and -*tert.*-amyl-sulphonium ions we have measured the total unimolecular rates, and also the proportions of olefin formed under the conditions of the rate measurements, thus deriving the separate rates of unimolecular substitution and elimination.

Whilst unimolecular olefin elimination (*E*1) from the *tert.*-butylsulphonium ion is a single process, the corresponding reaction of the *tert.*-amylsulphonium ion proceeds in two directions, just as does bimolecular elimination, producing a mixture of trimethylethylene and 1-methyl-1-ethylethylene. We have determined the proportions of these isomerides with the following results:

$$CH_3{\cdot}CH_2{>}C(CH_3)(CH_3){\cdot}\overset{+}{S}Me_2 \xrightarrow{(E1)} CH_3{\cdot}CH{=}C(CH_3)(CH_3)\ (87\%) + CH_3{\cdot}CH_2{>}C(CH_3){=}CH_2\ (13\%)$$

These figures refer to nearly neutral solution in " 97% " ethyl alcohol at 50°, *i.e.*, to conditions corresponding to those under which the total unimolecular rate constants and the proportions of total olefins, have been measured as recorded below. However, the ratio in which the two isomerides are produced in unimolecular elimination does not seem to be greatly affected by the conditions. For instance, in " 50% " ethyl alcohol (a mixture of equal volumes of alcohol and water), and at 65·3°, conditions corresponding to some measurements of the total unimolecular rate, and of the proportion of total olefin, which are recorded in Part VII, the trimethylethylene was found to constitute 85% of the total amylenes, the difference between this figure and the above-recorded 87% being almost within the normal experimental error. It will have been noticed that the proportions in which the isomeric amylenes are produced in the unimolecular elimination stand in marked contrast to those in which they are formed in bimolecular elimination from the dimethyl-*tert.*-amylsulphonium ion (14% of trimethylethylene). On the other hand, the proportions given by the unimolecular elimination are quite similar to those obtained for the corresponding unimolecular reaction of *tert.*-amyl bromide (82% of trimethylethylene—cf. Part XI).

Table IV contains the observational data by means of which dimethyl-*tert.*-butyl- and -*tert.*-amyl-sulphonium ions may be compared with respect to both the rates of their total unimolecular decompositions and the proportions in which total olefins are formed in these reactions.

TABLE IV.

First-order rate-constants (k_1 *in sec.*$^{-1}$) *and proportions of olefin formed in unimolecular reactions of tertiary alkyl-dimethylsulphonium iodides in "* 97% *" ethyl alcohol at* 50·0°.

Alk in $(AlkSMe_2)I$.	Initial concn. [$AlkSMe_2I$].	10^5k_1.	% Olefin.
tert.-Butyl	0·034 0·020	1·78 —	— 50·5
tert.-Amyl	0·034, 0·032 0·058	15·1, 14·8 —	— 64·5

These results are analysed in Table V, which records, for the two alkylsulphonium ions, the rates of the separate unimolecular reactions of substitution and of elimination, and also the rates with which the olefinic double bond is established in these eliminations along each of the three branches of the tertiary alkyl chains. In the theory of unimolecular reactions, a simple significance attaches to the rate of the total reaction, for this is identified with the rate of the common slow stage; and also to the proportions in which the olefins are formed, since these are interpreted as giving directly the ratios of the rates of the fast stages. Therefore these figures also are given in the Table, including the proportions in which the alkyl groups accept a double bond in each of their three branches.

TABLE V.

Analysis of kinetic data for the unimolecular reactions of tertiary alkyl-dimethylsulphonium ions in " 97% *" ethyl alcohol at* 50°, *showing the dependence of unimolecular elimination on alkyl structure.*

Alk in $AlkSMe_2$.	10^5k_1.	$10^5k(S_N1)$.	$10^5k(E1)$. Total.	$10^5k(E1)$. Per branch.	% Subn.	% Elimination. Total.	% Elimination. Per branch.
$\cdot C(CH_3)_2CH_3$	1·78	0·88	0·90	0·30 0·30 0·30	49·5	50·5	16·8 16·8 16·8
$\cdot C(CH_3\cdot CH_3)(CH_3)_2$	14·95	5·33	9·67	8·41 0·63 0·63	35·5	64·5	56·1 4·2 4·2

We may direct attention to the following relations. The rate of the total unimolecular reaction is considerably greater for *tert.*-amyl than for the *tert.*-butyl compound; and the difference is greater for the reactions of these sulphonium ions than it is for the corresponding reactions of the analogous tertiary alkyl halides (Part XI). The rate of unimolecular substitution is considerably increased, but the proportion of unimolecular substitution is decreased, in the *tert.*-amyl compound as compared with its lower homologue. The rate of unimolecular elimination is much greater for the *tert.*-amyl than for the *tert.*-butyl compound; and this is the total result of a large increase in the rate at which the olefinic double bond is established in that branch which becomes lengthened in the higher homologue, together with smaller increases in the rates at which it enters the branches that remain similar in the two compounds. The proportion of unimolecular elimination is greater for the *tert.*-amyl than for the *tert.*-butyl compound; and this is the net result of a considerable increase in the proportion in which the double bond is accepted into the lengthened chain of the amyl structure, partly counterbalanced by quite large decreases in the proportion in which it is established in the branches that remain similar in the two homologues. At almost every point, these relationships present marked contrasts to those which apply to the corresponding bimolecular reactions. On the other hand, except for the quantitative difference mentioned above, these relationships agree at every point with those which apply to the unimolecular reactions of *tert.*-butyl and *tert.*-amyl bromides (cf. Part XI). The theory of the matter will be considered in Part XVI.

EXPERIMENTAL.

Materials.—Freshly decolourised and distilled *tert.*-butyl iodide or *tert.*-amyl iodide was kept for 2 days at 20° in the dark with an equivalent of dimethyl sulphide in about 2 vols. of nitromethane as

solvent. The salt which first crystallised was washed with dry ether, and purified by partial precipitation from solution in ethyl alcohol by the addition of ether. Dimethyl-*tert.*-butylsulphonium iodide gave I = 51·9% (Calc.: I = 51·6%); dimethyl-*tert.*-amylsulphonium iodide gave I = 48·8% (Calc.: I = 48·8%). It was not advantageous to attempt to obtain further crops of these salts from the mother liquors, since the material thus recovered contained trimethylsulphonium iodide (cf. Part XII). The benzyl iodide employed in some of the separations was crystallised from alcohol at a low temperature, and thus obtained as colourless needles, m. p. 24°.

Methods for Measurement of Rates and Olefin Proportions.—These were as described in Part XII. The extraction method was used for the determination of *iso*butylene, and of the combined amylenes, aqueous mercuric chloride being employed for the purpose of removing organic sulphides (cf. Part VI). For unimolecular runs in acid solution, the formed olefin was determined at various times during the course of reaction, in order to control possible error arising from the acid-catalysed combination of the olefin with the solvent (cf. Part X). For runs in alkaline solution, and hence for all bimolecular runs, it was sufficient to determine the olefin formed towards the conclusion of the reaction.

Results of Measurements of Rates and Olefin Proportions.—The results of the principal series of measurements are given in Table I. In illustration of the experimental basis of these figures, we give in Tables VI, VII, and VIII the record of one bimolecular rate run, one unimolecular rate run, and one olefin determination. (As to the meaning of " 97% " EtOH, see footnote, p. 2086).

TABLE VI.

Illustrating determinations of total second-order rate-constants (k_2 *in sec.*$^{-1}$ *g.-mol.*$^{-1}$ *l.*): *Dimethyl-*tert.*-amylsulphonium iodide (Expt. A).*

(Solvent: " 97% " EtOH. Temp. 24·0°. Initially [SMe_2Am^tI] = 0·0910M and [NaOEt] = 0·234M. In the table [SMe_2Am^tI] and [NaOEt] are each expressed in c.c. of 0·2365N-acid per 15 c.c. sample.)

t (sec.).	[NaOEt].	[SMe_2Am^tI].	10^5k_2.	t (sec.).	[NaOEt].	[SMe_2Am^tI].	10^5k_2.
0	24·72	9·60	—	3582	21·19	6·07	59·5
509	24·23	9·11	56·4	4531	20·60	5·48	58·5
1143	23·30	8·18	58·9	5700	19·90	4·78	59·1
1812	22·78	7·61	56·8	9271	18·49	3·37	57·2
2403	22·13	7·01	59·4	12909	17·51	2·39	56·8

(Mean $k_2 = 58·1 \times 10^{-5}$ sec.$^{-1}$ g.-mol.$^{-1}$ l.)

TABLE VII.

Illustrating determinations of total first-order rate-constants (k_1 *in sec.*$^{-1}$): *Dimethyl-*tert.*-amylsulphonium iodide (Expt. A).*

(Solvent: " 97% " EtOH. Temp. 50·0°. Initially [SMe_2Am^tI] = 0·0340M. Solution initially neutral. Developed acid expressed in c.c. of 0·01655N-alkali per 10 c.c. sample.)

t (sec.).	Acid.	10^5k_1.	t (sec.).	Acid.	10^5k_1.	t (sec.).	Acid.	10^5k_1.
0	0·78	—	1926	6·07	15·5	6776	13·97	15·1
294	1·68	14·2	2614	7·52	15·8	8124	15·19	14·9
580	2·51	15·2	3802	10·63	17·1	9521	16·28	14·7
855	3·33	15·5	5811	12·45	14·4	∞	21·35	—

(Mean $k_1 = 15·1 \times 10^{-5}$ sec.$^{-1}$.)

TABLE VIII.

*Illustrating determinations of proportion of olefins formed: Total amylenes formed in unimolecular decomposition of dimethyl-*tert.*-amylsulphonium iodide.*

(Solvent: " 97% " EtOH. Temp. 50·0°. Initially [SMe_2Am^tI] = 0·0582M. Preliminary experiments had shown that after 30 minutes in these conditions a quantity of olefin convenient for measurement had been formed, but that it had not yet reacted to an appreciable extent with the solvent. Estimations of acid and olefin were therefore made at the time-zero and 30 minutes later. Samples of 15 c.c. were titrated with alkali, and, after addition of a standard quantity of bromine, with thiosulphate. The alkali and thiosulphate were standardised with reference to the same solution of potassium bi-iodate, KHI_2O_6; 25 c.c. of this required 4·97 c.c. of alkali, whilst 10 c.c. required 43·34 of the thiosulphate.)

Initial readings.		Readings after 30 mins.	
Alkali.	Thiosulphate.	Alkali.	Thiosulphate.
0·09	32·16	12·99, 12·93	2·30, 1·91
0·10	32·26	13·13	1·71

(Acid produced = 12·92 c.c. alkali. Olefin formed = 30·24 c.c. thiosulphate. Proportion of olefin = 64·5%.)

Experiments on the Isolation of Amylene Mixtures.—The first attempts to separate in a perfectly pure condition the amylenes formed from dimethyl-*tert.*-amylsulphonium salts, without disturbance

to the proportions of the isomerides, involved extracting the amylenes with tetrachloroethylene, after the addition of water to the alcoholic solution, and then removing the accompanying sulphides by extraction with aqueous mercuric chloride. This method failed, because it was found difficult to filter so great a bulk of the mercury compound without losses of, and therefore alterations to the composition of, the amylenes. The modification was therefore introduced of combining the sulphides with benzyl iodide, removing the easily filtered sulphonium salt, and ther eliminating the last traces of sulphides by the use of mercuric chlorides. The combination of benzyl iodide with the sulphides in the tetrachloroethylene solution was found to be considerably accelerated by the addition of some nitromethane. The experiment described below (Control No. 7) is one of several by which the reliability of this method was established.

Trimethylethylene has $n_D^{20°}$ 1·38774, and 1-methyl-1-ethylethylene has $n_D^{20°}$ 1·37774 (cf. Part XI). A mixture, 10 c.c., having $n_D^{20°}$ 1·38242, was added to 16 g. of dimethyl sulphide, 200 c.c. of ethyl alcohol, and 200 c.c. of water. The mixture was extracted with three 50 c.c. portions of tetrachloroethylene, and the combined extracts were mixed with 10 c.c. of nitromethane and 62 g. of benzyl iodide. The mixture was kept at 13° in the dark for 17 hours, and then filtered with the help of a pump, a liquid-air trap being used as a precaution against loss of the olefin. The salt on the filter was washed with a little pre-cooled tetrachloroethylene, and the combined filtrates were kept with 10 g. of mercuric chloride at − 10° overnight. Some calcium chloride was then added, and the mixture was kept at the same temperature for a further day, and then filtered through glass-wool. The filtrate was distilled, with a fairly high reflux ratio, through a well-lagged, 30 cm. column of Vigreux type, having only a small hold-up. The distillate up to 40° was collected. It had $n_D^{20°}$ 1·38231, and this figure was exactly repeated after the sample had been refluxed with, and distilled from, sodium–potassium alloy.

Analysis of Amylenes from the Bimolecular Reaction of Dimethyl-tert.*-amylsulphonium Ethoxide.*—The results have already been given, and the following details of one experiment are added as a description of method. A solution, 1·5 l., in " 97% " ethyl alcohol, 0·090M with respect to dimethyl-*tert.*-amylsulphonium iodide and 0·250N with respect to sodium ethoxide, was kept at 24° for 4 hours. It was then cooled to 0°, mixed with an equal quantity of water at 0°, and extracted with tetrachloroethylene, this procedure, and the subsequent treatment of the extract with nitromethane and benzyl iodide, and later with mercuric chloride and with calcium chloride, following exactly the lines of the control experiment already described. The distillate from the Vigreux column had $n_D^{20°}$ 1·37912. It was boiled under reflux for 30 minutes with sodium–potassium alloy, and again distilled. It then had $n_D^{20°}$ 1·37913, which corresponds to the composition, 14% trimethylethylene, 86% 1-methyl-1-ethylethylene.

Analysis of Amylenes from the Unimolecular Reaction of Dimethyl-tert.*-amylsulphonium Iodide.*—The following description illustrates the method used in these experiments. A solution, 1·5 l., in " 97% " ethyl alcohol, 0·255M with respect to dimethyl-*tert.*-amylsulphonium iodide, was coloured with cresol-red and heated at 50° for 7 hours in a flask fitted with a mercury-sealed stirrer, a reflux condenser, and a dropping funnel. A liquid-air trap was placed above the reflux condenser as a precaution against loss of olefin. A solution, about 1N with respect to sodium ethoxide, in " 97% " ethyl alcohol was run into the rapidly stirred solution of the sulphonium salt at such a rate as to maintain it either neutral or very faintly acid. At the end of the period mentioned the solution was cooled to 0°, and the amylenes were isolated as in the preceding example. The final product had $n_D^{20°}$ 1·38546, which corresponds to the composition 87% trimethylethylene, 13% 1-methyl-1-ethylethylene.

SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, January 15th,* 1948.]

---

425. *Mechanism of Elimination Reactions. Part XV. Olefin Elimination from* sec.-iso*Amyl Iodide and from the* sec.-iso*Amyl-dimethylsulphonium Ion.*

By E. D. HUGHES, C. K. INGOLD, and A. M. M. MANDOUR.

It is shown that methyl*iso*propylcarbinyl (*sec.-iso*amyl) iodide is decomposed by ethyl-alcoholic potassium hydroxide, in conditions determining the bimolecular mechanism of elimination, to give olefins in which the double bond becomes established mainly along the *iso*propyl branch, rather than along the methyl branch, of the secondary alkyl group; and also that the dimethyl-*sec.-iso*amylsulphonium ion is decomposed in aqueous solution in conditions favourable to the unimolecular mechanism to give an olefin mixture displaying the same kind of orientational effect in a quantitatively more extreme form. The former result confirms the conclusion, of which other evidence exists (Part X), that a non-terminal orientation of the double bonds is preferred in bimolecular eliminations of secondary alkyl halides, just as it has been shown to be in those of tertiary alkyl halides (Part XI). The latter result proves what has not been established elsewhere, namely, that a qualitatively similar orientation of the double bond is a property of unimolecular eliminations involving secondary alkyl groups, just as it is independently shown to be for corresponding reactions of tertiary alkyl groups (Parts XI and XIV).

THE experiments here reported were carried out in 1930, but were not published at the time because they did not appear to assist with the problem to the solution of which they were directed. As a matter of fact they could not so assist, because Organic Chemistry was not then

sufficiently advanced: the bimolecular and unimolecular mechanisms of substitution and elimination had not been discovered, and hyperconjugation was as yet unrecognised. Today, however, it is possible to attach significance to these early experimental results, which in effect extend certain later measurements reported in the preceding papers.

The problem which was thus prematurely attempted was that of the antithesis between Hofmann's rule of the preferential elimination of ethylene from quaternary ammonium salts and Saytzeff's rule for olefin elimination from secondary and tertiary alkyl halides—the situation being that Hofmann's rule agrees with, but Saytzeff's rule is contrary to, the theory of the inductive effect. We need neither go into the problem here, nor describe our incomplete working hypothesis of 1930 concerning a phenomenon the full explanation of which only became clear to us several years later; for in the next paper we shall state the problem and the explanation, since it will be our main purpose there to present the evidence on which our interpretation rests.

The experiments now to be described were on the lines of some which Lucas, Young, and their collaborators were carrying out at about the same period or a little earlier, and of others which we and our colleagues have since performed, on the compositions of the mixtures of isomeric olefins which are produced by the alkaline decompositions of branched-chain alkyl halides, or branched alkyl-dimethylsulphonium salts (cf. Parts X, XI, XIII, and XIV). In the present experiments an alkyl halide, and an alkyl-dimethylsulphonium ion having the same branched alkyl groups, were examined.

The study was concerned with the group *iso*propylmethylcarbinyl (*sec.-iso*amyl) $(CH_3)_2CH\cdot\dot{C}H(CH_3)$, and was directed to determining to what extent an olefinic double bond is accepted into the *iso*propyl branch, and to what extent into the methyl branch, when the group is eliminated as olefin by the alkaline decomposition of its iodide, or by decomposition of the related dimethylsulphonium hydroxide. The group was chosen as a secondary alkyl group in which the two branches present different numbers of β-hydrogen atoms, and thus permit the formation of olefins having different numbers of alkyl residues attached to the unsaturated carbon atoms. This particular alkyl group was selected with a view to avoiding the complication which made Lucas and Young's work, and also some of ours, difficult, namely, that of having to deal with a type of olefin one of the position-isomerides of which has two stereoisomeric modifications—with the result that a mixture of three closely similar olefins requires to be analysed. The methyl*iso*propylcarbinyl group is the simplest secondary alkyl group which can give two, but no more than two, olefins. They are trimethylethylene and *iso*propylethylene; and the binary mixtures of these isomerides can be accurately analysed, without the use of large quantities, by measurement of a suitable physical property, *e.g.*, the refractive index.

The decomposition of *sec.-iso*amylcarbinyl iodide was effected with the aid of concentrated ethyl-alcoholic potassium hydroxide. Although we had no appreciation of the importance of the point at the time, it is now quite clear, from the kinetics work described in Part X, that the bimolecular mechanism, *E*2, must have been in exclusive control. The results are shown in the following scheme:

$$(CH_3)_2CH\cdot CH_2\cdot CHI \xrightarrow[(E2)]{\bar{O}Et} (CH_3)_2C{=}CH_2\ (82\%) + (CH_3)_2CH\cdot CH{=}CH_2\ (18\%)$$

These analytical data are probably good to 1%. Comparison may be made with the figures obtained under similar conditions by Lucas and his collaborators, and again by Woolf (cf. Part X), for the lower-homologous *sec.*-butyl bromide:

$$CH_3\cdot CH_2\cdot CHBr\cdot CH_3 \xrightarrow[(E2)]{\bar{O}Et} CH_3\cdot CH{=}CH\cdot CH_3\ (81\%) + CH_3\cdot CH_2\cdot CH{=}CH_2\ (19\%)$$

We should have expected the two sets of data to fall as they actually do, but perhaps a little further apart. However, the figures last given depend, as has been mentioned, on a difficult analysis, and may be in error by 3%.

The decomposition of the dimethyl-*sec.-iso*amylsulphonium ion was carried out in a dilute aqueous solution, which was alkaline, but contained no alkali in excess over the sulphonium ion. It is obvious from our present knowledge of the kinetics of the aqueous decompositions of secondary alkyl-sulphonium ions (cf. Gleave, Hughes, and Ingold, *J.*, 1935, 236) that the unimolecular elimination mechanism, *E*1, must have been in practically exclusive control. The results themselves confirm this. For instance, the total yield of olefin was 7%; and that is

what it should be if the decomposition were unimolecular (cf. Part X, Table III *); whereas a yield of the order of 60% would have been produced if the reaction had been bimolecular (cf. Part XIII, Table I). The proportions of the isomerides, which are as follows, confirm the same conclusion :

$$(CH_3)_2CH\!>\!CH\cdot\overset{+}{S}Me_2 \xrightarrow[(E1)]{} (CH_3)_2C\!=\!CH\ (91\%) + (CH_3)_2CH\!-\!CH_2\!>\!CH\ (9\%)$$

In a bimolecular decomposition the above proportions would be approximately reversed, so that what is here the minor isomeride would become the major one. This will be evident from the results of Parts XIII and XIV.

We do not possess any directly determined figures for the proportions in which the isomeric olefins are formed in the unimolecular decompositions of the lower-homologous, *sec.*-butylsulphonium ion, or for the proportions in which they are formed in the unimolecular reaction of *sec.*-butyl bromide—a datum that would be equivalent, since both decompositions proceed through the same carbonium ion (cf. Part VI). The difficulty has been that the small yield (8%) of total olefins formed in the unimolecular reactions of these secondary alkyl compounds did not in our hands produce samples large enough for the satisfactory analysis of a ternary mixture of olefins (cf. Part X). This difficulty did not arise in the *sec.*-*iso*amyl example, which was so chosen that the formed olefin mixtures would be binary, and a comparatively small sample sufficient for analysis. However, we can estimate the proportions in which the olefins should be formed in the unimolecular decomposition of a *sec.*-butyl halide or sulphonium ion, on the basis of certain measured proportions for tertiary alkyl compounds. In the bimolecular reaction of *tert.*-amyl bromide with ethoxide ions, the amylene with a terminal double bond is produced to the extent of 29% of the total amylenes. In the unimolecular reaction of *tert.*-amyl bromide, or in that of the dimethyl-*tert.*-amylsulphonium ion, the proportion of this amylene is reduced to $16 \pm 2\%$ (Parts XI and XIV). In the bimolecular reaction of *sec.*-butyl bromide with ethoxide ion, the butylene with a terminal double bond is formed to the extent of 19% of the total butylenes (Part X). Hence we should expect that, in the unimolecular reaction either of *sec.*-butyl bromide, or of the dimethyl-*sec.*-butylsulphonium ion, the proportion of the terminally unsaturated butylene would be reduced in roughly the same ratio, *i.e.*, to $11 \pm 1\%$. Thus we can predict as follows :

$$CH_3\cdot CH_2\!>\!CH\cdot\overset{+}{S}Me_2 \xrightarrow[(E1)]{} CH_3\cdot CH\!=\!CH\ (89\%^*) + CH_3\cdot CH_2\!>\!CH_2\ (11\%^*)$$

(* Roughly estimated from data on other compounds.)

The corresponding figures for the reaction of the dimethyl-*sec.*-*iso*amylsulphonium ion should be similar, but a little more spread apart, just as in fact the determined figures are (see above).

The composition of the olefins formed in the unimolecular reaction of the *sec.*-*iso*amylsulphonium ion shows that unimolecular elimination from secondary alkyl-sulphonium salts corresponds to Saytzeff's rule. This, though it follows indirectly from the rate data reported in Part X, has not elsewhere been directly proved. The analytical data recorded in Part XIV show directly that unimolecular elimination from tertiary alkyl-sulphonium ions corresponds to Saytzeff's rule. Thus the present work establishes that there is no difference between the unimolecular reactions of secondary and tertiary alkyl groups in this respect.

In view of the results and conclusions of Part VI, the olefin compositions for the unimolecular decomposition of the *sec.*-*iso*amylsulphonium ion should apply equally to the unimolecular reactions of the *sec.*-*iso*amyl halides, and, in particular, to that of the iodide. On comparing this olefin composition with the above recorded composition of the olefins obtained in the bimolecular decomposition of *sec.*-*iso*amyl iodide, one observes that, whilst both bi- and uni-molecular elimination from this secondary alkyl halide follow the Saytzeff rule, the unimolecular reaction exhibits more strongly the particular type of orientation which the rule specifies. Quite similar conclusions follow from the analytical data, recorded in Part XI, concerning the olefins formed in the bi- and uni-molecular decompositions of *tert.*-amyl bromide. In this matter also, the present work establishes that secondary and tertiary alkyl groups act alike.

* It is true that this Table refers to alkyl bromides; but then the yield in which olefins are formed in the unimolecular decompositions of alkyl halides and alkyl-sulphonium ions with the same alkyl group under the same conditions should be almost the same, since the reactions proceed through the same carbonium ion; and in fact, the yields have been found to be nearly the same in the investigated examples (cf. Part VI, Table I).

The work described in Parts X, XI, XIII, and XIV has yielded data on the proportions in which isomeric olefins are formed in certain bimolecular eliminations involving secondary and tertiary alkyl halides and sulphonium ions; and also on unimolecular elimination from certain tertiary alkyl compounds. The work now recorded completes a series, inasmuch as it provides a direct determination, the only one so far made, of the proportions in which isomeric olefins are produced in unimolecular elimination from a secondary alkyl compound.

Experimental.

Materials.—Trimethylethylene was obtained by distilling a commercial sample, through a column, to constant b. p. (36°). *iso*Propylethylene was prepared from carefully purified *iso*amyl alcohol, by conversion into the iodide, and treatment of the latter with hot, saturated, ethyl-alcoholic potassium hydroxide. The resulting hydrocarbon was purified by being kept in contact, with frequent shaking for 2 hours at 0°, with twice its volume of concentrated aqueous sulphuric acid (2 vols. of sulphuric acid + 1 vol. of water). After being dried with sodium, it had b. p. 21·5°. *sec.-iso*Amyl iodide was prepared from this hydrocarbon by keeping it overnight at 20° with a saturated solution of hydrogen iodide in glacial acetic acid. The oil was separated and distilled (b. p. 135—139°); and the distillate was shaken for 2 hours at 20° with a large excess of water, and then for 2 hours with a further quantity of water. The iodide was finally washed with dilute aqueous sodium hydroxide, dried, and distilled (b. p. 138—139°). The *sec.-iso*amyl iodide was allowed to combine with dimethyl sulphide in solution in methyl cyanide at 30° for 10 days. The separated salt (yield 60—70%) consisted essentially (analysis) of dimethyl-*sec.-iso*amylsulphonium iodide contaminated with some trimethylsulphonium iodide. This contaminant we did not remove, since it seemed a difficult thing to do, and it could not interfere with the formation or isolation of the amylenes, as described below.

Olefin Elimination from sec.-iso*Amyl Iodide.*—The iodide was dropped on to boiling, saturated, ethyl-alcoholic potassium hydroxide. The hydrocarbons, after passing through a reflux condenser at 40°, water at 40°, and drying tubes of potassium carbonate at 40°, were condensed at −80°. The last traces of the hydrocarbon were carried over in nitrogen, after addition of some water to the boiling alkaline solution. After being finally dried with sodium, the amylene mixture, which was distilled completely without a column, had b. p. 23—35°.

*Olefin Elimination from Dimethyl-*sec.-iso*amylsulphonium Hydroxide.*—An aqueous solution of the dimethyl-*sec.-iso*amylsulphonium iodide was treated with a small excess of silver oxide. The filtered solution was distilled, using an all-glass apparatus, into a cooled receiver, where it was treated with a quantity of aqueous mercuric chloride more than sufficient to absorb the sulphides. From this receiver the amylenes were drawn by pumping, in a slow stream of air, through two further traps containing mercuric chloride solution, through calcium chloride and phosphoric anhydride, and into a receiver cooled in liquid air. The product was quite free from sulphides. After being kept for some time in contact with sodium, it was distilled completely without a column. The yield was 6·6%, calculated on pure dimethyl-*sec.-iso*amylsulphonium iodide.

Analysis of the Olefin Mixtures.—The refractive indices required for the analysis of the amylenes derived from *sec.-iso*amyl iodide were measured at 12·5° with the aid of a modified Pulfrich refractometer (60° prism), by Bellingham and Stanley, belonging to the University of Leeds. The refractive indices (λ Hg 5461 A.) were as follows: trimethylethylene, 1·33966; *iso*propylethylene, 1·32027; mixture, 1·33615. The composition of the mixture is thus: trimethylethylene, 81·9%; *iso*propylethylene, 18·1%. By the courtesy of Sir Jack Drummond, the measurements of refractive index needed for the analysis of the amylene mixture derived from dimethyl-*sec.-iso*amylsulphonium hydroxide were made at 4° in a cold-room in the Department of Biochemistry of University College, London. In this case an ordinary Pulfrich instrument was used, and observed angles were used directly for the interpolation required to give the composition of the mixture. The angles (λ Hg 5461 A.) were as follows: trimethylethylene, 0° 0′ 36″; *iso*propylethylene, 3° 13′ 18″; mixture, 0° 17′ 12″. The resulting composition is as follows: trimethylethylene, 91·4%; *iso*propylethylene, 8·6%.

The University, Leeds.
University College, London, W.C.1.

[*Received, January 15th,* 1948.]

---

426. *Mechanism of Elimination Reactions. Part XVI. Constitutional Influences in Elimination. A General Discussion.*

By M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw, and L. I. Woolf.

Classical organic chemistry has provided two empirical rules for the orientation of elimination, the Hofmann rule, that tetra-alkylammonium ions give the least alkylated ethylene, and the Saytzeff rule that alkyl halides produce the most alkylated ethylene. These antithetical rules are reconciled on the basis that they signalise different internal processes of electron displacement, which appear at different times during an individual molecular act of elimination, and are energised from independent sources. The detailed theory involves the correlation of orientation with reaction rate and kinetic type, and the fitting of constitutional effects on all these phenomena into the framework of the established mechanisms of elimination.

The Hofmann rule is part of a broader pattern of constitutional effects, which can all be consistently interpreted as the control of elimination by inductive electron-displacement. The effect depends on the polarity of substituents, and their consequent ability to create a positive electrical field at the β-carbon atom. Amongst alkyl compounds, control by the inductive effect is dominating for bimolecular eliminations when the electron-attracting substituent, Y in $HC_\beta \cdot C_\alpha Y$, carries a positive ionic charge. Substituents of sufficient polarity will, however, exert a dominating inductive effect on elimination in any system.

The Saytzeff rule is a part of another general pattern of structural effects, all of which can be consistently interpreted as the control of elimination by electromeric electron-displacement. This effect depends on the unsaturation of substituents, and their consequent ability to conjugate or hyperconjugate with the developing olefinic double bond, $C_\beta{:}C_\alpha$. Amorgst alkyl compounds, control by the electromeric effect is dominating in bimolecular eliminations when the electron-attracting group Y is uncharged; and in all unimolecular eliminations. Substituents of sufficient unsaturation will, however, exert a dominating electromeric effect on elimination in any system.

The inductive effect is a polarisation, exerted from the commencement of reaction; but the electromeric effect is a polarisability effect, which is developed during reaction, and achieves its main kinetic importance in the transition state of olefin formation. The inductive effect is driven by the Coulomb forces of classical electrostatic polarity; but the electromeric effect is energised independently by the quantal resonance of electrons having properties of unsaturation. The polarity and unsaturation of alkyl groups are especially considered, and the concept of hyperconjugation is broadened.

Steric factors may limit the free operation of these polar constitutional influences. The most important steric restriction on elimination is that the β-CH electrons in $HC_\beta \cdot C_\alpha \cdot Y$ must enter the octet of C_α on the side remote from Y. This applies only to bimolecular elimination; but it then applies no matter whether Y is a formally neutral group, or whether it carries a positive ionic charge. The requirement arises from the need to economise energy by minimising bond-overlap in the transition state of elimination.

This discussion of constitutional effects on heterolytic 1 : 2-elimination is complementary to a discussion of environmental effects already given in Part V and supplemented in Parts VII and VIII.

(1) Mechanisms of Elimination.

Any reaction of the form

$$X{-}a{-}b{-}Y \longrightarrow \overset{+}{X} + a{=}b + \bar{Y}$$

where X separates without the electrons which it shared with *a*, and Y with those which it shared with *b*, X and Y being otherwise unrestricted as to charge, may be designated a heterolytic 1 : 2-elimination. The context admitting no ambiguity, we shall often hereafter refer to such a reaction simply as an elimination.

We are to discuss constitutional effects on heterolytic 1 : 2-eliminations. Any theory of such constitutional effects must be fitted into an established framework of reaction mechanism. Therefore we shall first consider the nature and range of application of the mechanisms known to be available.

(1.1) *Bimolecular Mechanism* (E2).—This was first recognised as a general mechanism of elimination by Hanhart and Ingold in 1927. It is the most widespread of elimination mechanisms. It may be described for the case in which X is a hydrogen, and *a* and *b* are carbon atoms, since this is the most common case, though other possibilities for all these atoms exist as will be mentioned later. In the case specified, a reagent Z possessing nucleophilic (in particular basic) properties extracts the protonic part of a combined hydrogen atom, while an electron-attracting group Y simultaneously separates in possession of its previously shared electrons. A co-operative effect arises in 1 : 2-elimination by this mechanism, since the hydrogen atom and the electron-attractor are bound to adjacent atoms, and therefore atomic electron shells may remain complete throughout the change, without any alteration of the carbon frame. Two bonds are broken, but each fission assists the other, the two together constituting a single synchronised act. The mechanism may be formulated thus,

$$Z + H{-}\overset{\curvearrowright}{C}R_2{-}\overset{\curvearrowright}{C}R_2{-}Y \longrightarrow ZH + CR_2{:}CR_2 + Y \quad (E2)$$

the arrows showing how the charges on Z and Y are changed, though for the charges themselves there are several possibilities.

The consequences of the bimolecular mechanism have up to the present been illustrated with respect to the formation of olefins from tetra-alkylammonium salts, certain specially chosen tetra-alkylphosphonium salts, trialkylsulphonium salts, dialkyl and aryl alkyl sulphones, and alkyl halides. The mechanism has also been made probable for alkyl sulphonates and

certain alkyl carboxylates. Neutral or negatively charged reagents, varying in basicity from water to ethoxide and amide ions, have been employed :

$$\cdot Y = \cdot\overset{+}{N}R_3,\ \cdot\overset{+}{P}R_3,\ \cdot\overset{+}{S}R_2,\ \cdot SO_2R,\ \cdot Cl,\ \cdot Br,\ \cdot I,\ \cdot O\cdot SO_2R,\ \cdot O\cdot COR$$

$$Z = OH_2,\ NMe_3,\ \bar{O}Ac,\ \bar{O}\cdot C_6H_4\cdot NO_2,\ \bar{O}Ph,\ \bar{O}H,\ \bar{O}Et,\ \bar{C}O_3,\ \bar{N}H_2$$

The following reactions are typical of those which have been investigated in this connexion (cf. p. 2096) :

$$NMe_3 + CH_2Ar\cdot CH_2\cdot\overset{+}{N}Me_3 \longrightarrow \overset{+}{N}HMe_3 + CHAr{:}CH_2 + NMe_3$$

$$\bar{O}H + CH_3\cdot CH_2\cdot\overset{+}{S}Me_2 \longrightarrow OH_2 + CH_2{:}CH_2 + SMe_2$$

$$\bar{O}H + CH_3\cdot CH_2\cdot SO_2\cdot Et \longrightarrow OH_2 + CH_2{:}CH_2 + \bar{S}O_2Et$$

$$\bar{O}Et + CH_2Ar\cdot CH_2Br \longrightarrow HOEt + CHAr{:}CH_2 + \bar{B}r$$

To these examples we may first add two others, chosen because they show that conditions similar to those required for the bimolecular formation of the double bond C:C by olefin elimination also apply to the formation of the double bonds C:N and N:N by corresponding elimination processes :

$$\bar{O}H + Ph\cdot CH_2\cdot NMe\cdot SO_2Ar \longrightarrow OH_2 + Ph\cdot CH{:}NMe + \bar{S}O_2Ar$$

$$\bar{O}Et + Ac\cdot NH\cdot NH\cdot SO_2Ar \longrightarrow HOEt + Ac\cdot N{:}NH + \bar{S}O_2Ar$$

The first of these equations expresses the hydrolysis of a sulphonamide, containing a suitably disposed hydrogen atom, by means of concentrated alkali, to a sulphinic acid and a Schiff's base (instead of, as might be thought normal, to a sulphonic acid and an amine). The second equation, together with the presumed decomposition $AcN_2H \longrightarrow AcH + N_2$, constitutes a representation of McFadyen and Stevens's method of converting a carboxylic acid into the corresponding aldehyde by alkaline alcoholysis of a sulphonyl derivative of the acid hydrazide. We give one more example, which is due to Sommers and Whitmore :

$$\bar{O}H + SiCl_3\cdot CH_2\cdot CH_2Cl \longrightarrow HO\cdot SiCl_3 + CH_2{:}CH_2 + \bar{C}l$$

It is mentioned in order to illustrate the point that other groups than hydrogen may have a sufficient affinity for a strongly nucleophilic reagent to fulfil the same function as that which hydrogen often fulfils in the general reaction. (In practice, the compound $HO\cdot SiCl_3$ is hydrolysed to silicic acid.)

The originally advanced evidence of mechanism was largely circumstantial : it had reference to the conditions and course of the reaction, especially the obvious need for a strong base. Much firmer evidence has been supplied since by the use of reaction kinetics and of the isotopic indicator method.

Eliminations which proceed by the bimolecular mechanism normally exhibit second-order kinetics. Such kinetics have been formally established in representative cases extending over the following range of variation of the electron-attracting group Y and the basic reagent Z :

$$\cdot Y = \cdot\overset{+}{N}R_3,\ \cdot\overset{+}{S}R_2,\ \cdot Cl,\ \cdot Br,\ \cdot I$$

$$Z = \bar{O}H,\ \bar{O}Et$$

However, just as with bimolecular nucleophilic substitution, this correspondence between mechanism and reaction order is not universal. In the investigated cases of it, a strongly basic reagent is employed, as in the following example ($Ar = C_6H_5$) :

$$\bar{O}H + Ar\cdot CH_2\cdot CH_2\cdot\overset{+}{N}Me_3 \longrightarrow OH_2 + Ar\cdot CH{:}CH_2 + NMe_3 \qquad (E2;\ \text{2nd order})$$

But if the vulnerable hydrogen atom is further activated by an appropriate constitutional change, a much weaker base will suffice; and that may be a solvent molecule. If, in the above example, a *p*-nitro-group is introduced into the 2-phenylethylammonium ion, the following reaction will take place, which is of the first order in aqueous solution ($Ar = p\text{-}C_6H_4\cdot NO_2$) :

$$OH_2 + Ar\cdot CH_2\cdot CH_2\cdot\overset{+}{N}Me_3 \longrightarrow \overset{+}{O}H_2 + Ar\cdot CH{:}CH_2 + NMe_3 \qquad (E2;\ \text{1st order})$$

In spite of its kinetic order, this reaction is undoubtedly bimolecular in mechanism, as is shown by the large increases of speed which are observed when small amounts of some stronger base

than water are added initially. (Kinetic complications do not arise from the production of the base NMe_3, because this accepts a proton from the simultaneously formed $\overset{+}{O}H_3$, thus instantly losing its basic properties.)

Although the kinetic results are consistent with the bimolecular mechanism, they do not of themselves exclude a two-stage process, in which the basic reagent first extracts a proton from the alkyl compound, leaving an anionic form, which then suffers unimolecular change with loss of the electron-attracting group. This possibility has, however, been excluded by Skell and Hauser, by examination of the following reaction in " heavy " alcohol, EtOD, as solvent :

$$\bar{O}Et + Ph{\cdot}CH_2{\cdot}CH_2Br \longrightarrow HOEt + Ph{\cdot}CH{:}CH_2 + \bar{B}r$$

They showed that 2-phenylethyl bromide, isolated after the reaction had proceeded part way, contained no deuterium, and that therefore the anionic form $\bar{C}HPh{\cdot}CH_2Br$ could not have been produced as an intermediate product.

Sectional Summary.—This Section surveys the evidence for, and established range of application of, the bimolecular mechanism of elimination.

References.—(a) *Ammonium salts.* (1) Hanhart and Ingold, *J.*, 1927, 997; (2) Ingold and Vass, *J.*, 1928, 3125; (3) v. Braun, Teuffert, and Weissbach, *Annalen*, 1929, **472**, 121; (4) v. Braun and Buchmann, *Ber.*, 1931, **64**, 2610; (5) v. Braun and Hamann, *Ber.*, 1932, **65**, 1580; (6) Ingold and Patel, *J.*, 1933, **68**; (7) Hughes and Ingold, *ibid.*, p. 523; (8) Hughes, Ingold, and Patel, *ibid.*, p. 526; (9) Part VII, this vol., p. 2043.

(b) *Phosphonium salts.* (10) Fenton and Ingold, *J.*, 1929, 2342; (11) Hey and Ingold, *J.*, 1933, 531.

(c) *Sulphonium salts.* (12) Green and Sutherland, *J.*, 1911, **99**, 1174; (13) Ingold, Jessop, Kuriyan, and Mandour, *J.*, 1933, 533; (14) Ingold and Kuriyan, *ibid.*, p. 991; (15) Hughes and Ingold, *ibid.*, p. 1571; (16) Gleave, Hughes, and Ingold, *J.*, 1935, 236; (17) Part VIII, this vol., p. 2049; (18—21) Parts XII—XV, this vol., p. 2072 *et seq.* Cf. also refs. 3 and 9.

(d) *Sulphones.* (22) Fenton and Ingold, *J.*, 1928, 3127; (23) *idem*, *J.*, 1929, 2338; (24) *idem*, *J.*, 1930, 705.

(e) *Halides.* (25) Olivier and Weber, *Rec. Trav. chim.*, 1934, **53**, 1087, 1093; (26) Hughes, *J. Amer. Chem. Soc.*, 1935, **57**, 708; (27) Hughes and Ingold, *J.*, 1935, 244; (28) Hughes, Ingold, and Shapiro, *J.*, 1936, 225; (29) Hughes and Shapiro, *J.*, 1937, 1177; (30) *idem*, p. 1192; (31) Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 899; (32—34) Parts IX—XI, this vol., p. 2055 *et seq.* Cf. also refs. 9 and 17.

(f) *Esters.* (35) W. Hückel, Tappe, and Legutke, *Annalen*, 1940, **543**, 191; (36) Hauser, Shivers, and Skell, *J. Amer. Chem. Soc.*, 1945, **67**, 409.

(g) *Sulphonamides.* (37) Holmes and Ingold, *J.*, 1926, 1305.

(h) *Sulphonhydrazides.* (38) McFadyen and Stevens, *J.*, 1936, 584.

(i) $SiCl_3$-*substituted halides.* (39) Sommers and Whitmore, *J. Amer. Chem. Soc.*, 1946, **68**, 485; (40) Sommers, Goldberg, Dorfman, and Whitmore, *ibid.*, p. 1083.

(j) *Reaction kinetics.* Cf. refs. 7, 9, 12, 15—21, and 28—34.

(k) *Isotopic indicator.* (41) Skell and Hauser, *J. Amer. Chem. Soc.*, 1945, **67**, 1661.

(1.2) *Unimolecular Mechanism* (E1).—This process was signalised as a general mechanism by Hughes in 1935. It is known as yet only for the important case in which X is a hydrogen atom, and *a* and *b* are carbon atoms. Its main characteristic is that the electron-attracting group Y breaks away without the co-operation of the proton-extracting reagent Z, leaving a carbonium ion, which subsequently loses a proton to the solvent or some other proton acceptor. The reaction thus has two stages, of which the first, the heterolytic separation of Y, is rate-determining; so that the rate of the overall reaction is independent of any added base. The mechanism may be formulated thus,

$$\left.\begin{array}{l} H{-}CR_2{-}CR_2{-}Y \xrightarrow[\text{slow}]{} H{-}CR_2{-}\overset{+}{C}R_2 + Y \\ H{-}CR_2{-}\overset{+}{C}R_2 \xrightarrow[\text{fast}]{} \overset{+}{H} + CR_2{:}CR_2 \end{array}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (E1)$$

where the group Y may be either formally neutral or positively charged before reaction, becoming, as the case may be, either negatively charged or neutral afterwards.

Up to the present this mechanism has been established (in one case, made probable) over the following range of electron-attracting groups :

$$\cdot Y = \cdot\overset{+}{S}R_2,\ \cdot Cl,\ \cdot Br,\ \cdot I,\ \cdot O{\cdot}SO_2R$$

Two illustrations may be given of eliminations for which this mechanism is prominent :

$$CH_3{\cdot}CMe_2Br \longrightarrow \overset{+}{H} + CH_2{:}CMe_2 + \bar{B}r$$

$$CH_3{\cdot}CMe_2{\cdot}\overset{+}{S}Me_2 \longrightarrow \overset{+}{H} + CH_2{:}CMe_2 + SMe_2$$

Our evidence of this mechanism is derived mainly from the study of the reaction kinetics, particularly with reference to its insensitiveness to bases, its relation to concurrent unimolecular substitution, and its orientation.

We may emphasise the generality of what has been pointed out in particular cases before, *viz.*, that the bi- and uni-molecular mechanisms, *E*2 and *E*1, must merge into each other. For in mechanism *E*2 the attack of Z assists the separation of Y, whereas in mechanism *E*1 the reagent Z gives no such aid; and there must be a wide range of degrees of assistance which Y might require and a suitable Z could render.

Sectional Summary.—This Section surveys the evidence for, and the established range of application of, the unimolecular mechanism of elimination.

References.—(a) *Halides.* (26) Hughes, *loc. cit.*; (42) Hughes, Ingold, and Scott, *Nature*, 1936, **138**, 120; (43) *idem*, *J.*, 1937, 1271; (44) Hughes, Ingold, and Shapiro, *J.*, 1937, 1277; (45) Cooper, Hughes, and Ingold, *J.*, 1937, 1280; (46) Hughes, Ingold, and MacNulty, *J.*, 1937, 1283. Cf. also refs. 9, 17, 21, 33, and 34.
(b) *Sulphonium salts.* (47) Part VI, this vol., p. 2038. Cf. also refs. 9, 17, 20, and 21.
(c) *Sulphonic esters.* (48) W. Hückel and Tappe, *Annalen*, 1939, **537**, 113. Cf. also ref. 35.
(d) *Reaction kinetics.* Cf. refs. 9, 17, 20, 21, 33, 42, 43, 44, and 45.

(2) Empirical Orientation Rules and their General Significance.

During the classical period of organic chemistry, a peculiar situation arose in relation to the rules which summarised empirical knowledge concerning the orientation of elimination. We shall sketch this situation in the present Section, since an important part of the problem with which we were confronted was that of fitting it into the mechanistic framework outlined in Section 1.

It was observed by Hofmann (*Annalen*, 1851, **78**, 253; **79**, 11) that when a quaternary ammonium hydroxide contains different primary alkyl radicals, so that various olefins might be produced by decomposition in different directions, the principal olefin to be formed in the actual decomposition of the quaternary compound is always ethylene if an ethyl group is present. Though originally given with the limitations stated, this rule has since, by an obvious generalisation, been taken to require the preferential formation, from a quaternary ammonium hydroxide containing only primary alkyl groups, of that ethylene which carries the *smallest* number of alkyl substituents.

It was pointed out by Saytzeff (*Annalen*, 1875, **179**, 296) that, of the isomeric olefins which could be formed from a secondary or tertiary alkyl halide by elimination in the different branches of the alkyl chain, the one actually produced in greatest proportion is determined by the condition that the eliminated hydrogen atom is lost preferentially from that carbon atom which bears the smallest number of hydrogen atoms. An equivalent expression of the same rule is that it requires the preferential production, from a secondary or tertiary alkyl halide, of that ethylene which carries the *largest* number of alkyl substituents.

So long as Hofmann's and Saytzeff's rules were regarded as merely expressing the observed effects of unknown causes in unrelated fields of organic chemistry, their antithetical relation to each other was hardly noticed. But after Hanhart and Ingold had given a treatment of the decompositions of quaternary ammonium compounds which placed the reactions of those substances in the same class as those of alkyl halides, then it at once became a challenge to discover why two contradictory rules, jointly summarising all that was known about the orientation of elimination, should govern different applications of the same general reaction.

From the outset of this enquiry our basic assumption has been that the co-existence of two antithetical orientation rules betrays the presence of two internal orientational processes. Each may well require a different set of systemic conditions for its most effective operation. Each will certainly be driven forward by a diffreent set of forces. It is fundamental to this general picture that the two sources of energy shall be independent each of the other, in order that the two processes may be able to work in the same system, without mutual interference, and either in conjunction or in opposition.

Already in 1930, when this work was begun (preceding paper), a somewhat similar position had arisen with reference to another group of organic reactions; and it was then in the process of being interpreted. The reactions were those of aromatic substitution; and we shall here recall what happened in that matter, because it provides a helpful analogy with the problem with which we have to deal concerning the orientation of eliminations. Two partly contrary orientation rules of aromatic substitution had been recognised. A large class of substituents oriented further substitution, either to the ortho- and para-, or to the meta-positions, according

to the direction of the dipole associated with the link between the substituent and the aromatic ring. Another class of substituents, those connected to the ring through a negative or neutral atom having unshared electrons, directed uniformly towards the ortho- and para-positions, even when such orientation was contrary, as in most cases it was, to the effect to be expected from the direction of the link dipole.

The first step in the interpretation involved associating each of the rules of orientation with a separate form of electron displacement. The second step was to show, through a combined study of the orientation and velocity of substitution, that the two effects to a large extent enter at different stages during any individual molecular act of substitution. Putting these two points together, the conclusion was that inductive electron displacement is responsible for the orientation connected with the link dipole, and is largely a polarisation, *i.e.*, a displacement which is prominent in the initial state of the reacting system; but that electromeric electron displacement produces the orientation originating in the unshared electrons, and is mainly a polarisability effect, *i.e.*, a displacement which belongs chiefly to the transition state of the reacting system. The third step in the interpretation, *viz.*, the recognition of the fundamental reason for the mutual independence of the two effects, was not completed until 1933, when it was shown that, whereas the forces driving the inductive effect are of the classical electrostatic type, the driving force behind the electromeric effect is basically non-classical, being of the same general nature as are the forces of exchange degeneracy in the theory of co-valency. That was the real reason why a substituent like chlorine could, in the same reaction, give rise to phenomena which suggested a simultaneous attraction and repulsion of electrons (Allen, Oxford, Robinson, and Smith, *J.*, 1926, 401; Ingold and Ingold, *ibid.*, p. 1310; Ingold and Shaw, *J.*, 1927, 2918; Ingold, *J.*, 1933, 1120).

This theory of aromatic substitution provides a very close parallel to the theory which we are going to build concerning elimination. Again we start with antithetical orientation rules. And in the interpretation we shall find the same two forms of electron displacement, the same kind of distinction between the time of appearance of each in the course of a molecular act of elimination, and that same sort of independence, of ability to work in opposite directions without mutual interference, which produces the *prima facie* impression of a group behaving towards electrons (and protons) in both of two inconsistent ways.

Sectional Summary.—The Hofmann and Saytzeff rules for the orientation of elimination are so antithetical as to suggest that they signalise internal processes of electron displacement which are energised in independent ways. The analogy of aromatic substitution is cited as a guide for the construction of a theory on these general lines.

(3) Orientation and Reaction Rate. More detailed Interpretation.

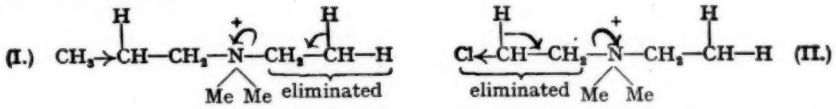
(3.1) *Bimolecular Elimination in 'Onium Ions : The Inductive Effect.*—The internal mechanism underlying Hofmann's rule was identified with the general inductive effect by Hanhart and Ingold. A heterolytic elimination always involves a strongly electron-attracting group, which, by inducing a positive charge on all the surrounding carbon atoms, loosens the protons, a sufficient loosening of a β-proton permitting the elimination mechanism *E*2. A group which, by releasing electrons, tends to neutralise the induced positive charge on the β-carbon atom, and thus to tighten its hold on the β-protons, will inhibit reaction. The terminal methyl radical of the *n*-propyl group acts in this way, and so determines that, in accordance with Hofmann's rule, the *n*-propyl group will show relatively little tendency to engage in an olefin-forming process if an ethyl group is available to fulfil this function (formula I, below).

Similarly, an *iso*butyl group will not participate to any great extent in elimination if a *n*-propyl group (still more, if an ethyl group) is available; and, naturally, the terminal methyl radicals in the *n*-propyl and *iso*butyl groups may be replaced by ethyl or higher homologous radicals without changing these comparisons. This is the generalised rule given in Section 2, which actually was obtained by Hanhart and Ingold from the theory, Hofmann's original empirical rule being recognised as a special case.

Further generalisation follows from the consideration that the protective electron displacement can be relayed to the β-carbon atom from non-adjacent atoms, but only with considerable loss of intensity. Thus the protective effect to be observed in the *n*-propyl group will be increased in the *n*-butyl group, but it will not be so great there as in the *iso*butyl group. In general the effect will increase with homology, tending to a limit but always subject to the condition that a branched-chain radical is more effective than the isomeric normal chain.

Outside the range of hydrocarbon radicals, we expect electron-attracting substituents to

promote elimination, and to do so with greatest effect if they are directly attached to the β-carbon atom (formula II).



With various degrees of elaboration and completeness, these deductions from theory have been tested and established for a number of primary alkyl and substituted alkyl groups, not only for ammonium hydroxides and ammonium ethoxides, but also for sulphonium hydroxides and for the alkali-promoted decompositions of sulphones (Section 1.1, refs. 1, 2, 6, 13, 14, 22, and 23).

Although the bimolecular mechanism was presupposed in the theory, no control over the reaction kinetics was established at the time of these experiments, the existence of the unimolecular mechanism of elimination being then unsuspected. However, the investigations were almost entirely concerned with alkaline decompositions involving primary alkyl groups, and subsequent research has shown that in these conditions the mechanism is in fact wholly bimolecular. The actual method of experiment was orientational, the measurement relating to the proportions in which products were formed in decompositions capable of proceeding in a number of alternative directions.

One form of the method was to place two olefin-forming alkyl groups in competition with each other in the same 'onium ion (or sulphone), as illustrated in the preceding formulæ. Using this method, it has been shown, for instance, that in the decompositions of sulphonium hydroxides the first four primary alkyl groups stand in the following order with respect to the facility with which they split off as olefins :

$$\text{ethyl} > n\text{-propyl} > n\text{-butyl} > iso\text{butyl}.$$

Another method of comparison employed 'onium ions containing only one olefin-yielding alkyl group, and otherwise only methyl groups. The basic assumption was that changes in the olefin-forming group would not much affect the tendency of a methyl group to split off in a substitution reaction. Accordingly, the success of the elimination with different olefin-forming groups, in competition with this more or less standard process of displacement of the methyl group, was taken as a measure of the intrinsic tendency of the variable alkyl group to yield an olefin. It was also assumed that the comparison would not be upset by any large tendency among the variable alkyl groups to be displaced by substitution, and that seems to be true to a fair degree of approximation. The decompositions of ammonium hydroxides, for instance, have been studied in this way, and the following primary alkyl groups have thus been placed in order with respect to the ease with which they yield olefins in this reaction :

$$\text{ethyl} > n\text{-propyl} > n\text{-butyl} > n\text{-amyl} \sim n\text{-octyl} > iso\text{amyl} > iso\text{butyl} > \psi\text{-hexyl}$$

After duality of mechanism for eliminations generally, and the consequent need for kinetic control, had been realised, it was felt desirable not only to confirm kinetically that the reactions studied are bimolecular, as those which produce olefin from primary alkyl groups in ammonium and sulphonium ions certainly are (Section 1.1, refs. j), but also to ascertain whether the rates of bimolecular olefin formation from such ions really do vary with homology in the sense indicated by theory, and by the experiments on orientation. For the simpler primary alkyl groups this has been done, and that part of the work which relates to sulphonium ions* is now published (Part XII). The results are consistent with theory, and with the orientational data. Thus the second-order rate-constants for the reaction

$$RR'CH\cdot CH_2\cdot\overset{+}{S}Me_2 + \bar{O}Et \longrightarrow HOEt + RR'C{:}CH_2 + SMe_2$$

where R, R′ = H, Me, Et, in dry ethyl alcohol at 64°, with sulphonium iodide and sodium ethoxide initially at concentrations 0·05 and 0·095M, respectively, are as follows [$k(E2)$ is in sec.$^{-1}$ g.-mol.$^{-1}$ l.] :

Alk in Alk$\overset{+}{S}$Me$_2$	Ethyl.	*n*-Propyl.	*n*-Butyl.	*iso*Butyl.
$10^5k(E2)$	60	27	17	14

The remarkable effect on rate which was observed (Part XII) with R = Ph will be considered in Section 3.4.

* The part which relates to ammonium ions is being developed as a study of salt effects, and is therefore not yet ready for publication.

At the outset of our work it was known that the Hofmann rule applied to primary alkyl groups in 'onium ions, and that the Saytzeff rule applied to secondary and tertiary alkyl groups in halides; but nobody knew whether the change of rule was due to the difference in the type of alkyl group, to the difference in the type of the electron-attracting group, or to a difference of mechanism. We therefore proceeded to delimit the possibilities by extending our study of the bimolecular mechanism of elimination to secondary and tertiary alkylsulphonium ions. These experiments had reference both to the orientation and the velocity of elimination, but even the orientation experiments were made under kinetically controlled conditions, a precaution which is certainly necessary when dealing with secondary and tertiary alkyl groups.

As to orientation, the answer for secondary alkyl groups is given by the following result for bimolecular elimination from the dimethyl-*sec.*-butylsulphonium ion (Part XIII):

$$\underset{+OEt^-}{CH_3\cdot CH_2\cdot CH(\overset{+}{S}Me_2)\cdot CH_3} \xrightarrow[(E2)]{} \underset{26\%}{CH_3\cdot CH{=}CH\cdot CH_3} + \underset{74\%}{CH_2\cdot CH_2\cdot CH{=}CH_2}$$

This is orientation according to the extended Hofmann rule, the principal olefinic product being the ethylene which carries the smaller number of alkyl substituents. It is theoretically explained by an assumed protection of the β-hydrogen atom in the longer branch of the *sec.*-butyl group by an electron-displacement from the terminal methyl substituent in that branch.

Reaction rates confirm this diagnosis. For the second-order rate-constants of the reaction

$$R\cdot CH_2\cdot CHMe\cdot\overset{+}{S}Me_2 + \bar{O}Et \longrightarrow HOEt + \text{Olefins} + SMe_2$$

with R = H, Me, in ethyl alcohol at 64°, and with salt concentrations 0·05 and 0·095M as before, the following values [$k(E2)$ in sec.$^{-1}$ g.-mol.$^{-1}$ l.] were found (Part XIII):

Alk in Alk$\overset{+}{S}$Me$_2$.....		*iso*Propyl.	*sec.*-Butyl.
$10^5k(E2)$: total	longer branch	1040 {520	695 {185
	shorter branch	520	510

It will be noticed that the higher homologous group gives olefin more slowly, as though the β-linked methyl substituent, which it contains, was producing a protecting effect. Further, practically the whole of the reduction of rate is due to the diminished rate of entry of the double bond into that alkyl branch which contains the β-methyl substituent, the rate of its entry into the other branch being almost unaffected. This shows that the protecting action is localised in the molecule, just as one would expect of the inductive electron displacement, which is postulated.

Even in the figures thus far quoted there is a warning that the theory of the Hofmann rule is not a complete theory of orientation and velocity in bimolecular elimination from primary and secondary alkyl-sulphonium ions. The secondary groups, *iso*propyl and *sec.*-butyl, differ from the primary groups, ethyl and *n*-propyl, respectively, in that the secondary groups possess an extra α-linked methyl substituent. According to the theory of the Hofmann rule, this extra substituent could exert some protective effect on the β-protons of the other branch of the secondary alkyl group; but it would be a small effect, not nearly as big as if the extra substituent were in the β-position, and therefore close to the β-protons. Thus, as compared with ethyl and *n*-propyl, respectively, we should expect olefin formation in those branches of *iso*propyl and *sec.*-butyl with respect to which the extra methyl group can be regarded as an α-substituent to proceed at a slightly reduced rate. Actually it proceeds at a considerably increased rate—a rate 7—9 times larger than in the absence of the α-methyl substituent. An enormously enlarged effect in the same direction is observed when we introduce an α-phenyl substituent (Part XIII). Obviously these α-substituents are acting in some way of which our theory has yet to take account: we shall consider what it is in Section 3.2, and discuss these particular applications in Section 3.4.

As to tertiary alkyl groups, the nature of the orientation governing bimolecular elimination from sulphonium ions is shown by the following result for the reaction of the dimethyl-*tert.*-amylsulphonium ion (Part XIV):

$$\underset{+OEt^-}{CH_3\cdot CH_2\cdot CMe(\overset{+}{S}Me_2)\cdot CH_3} \xrightarrow[(E2)]{} \underset{14\%}{CH_3\cdot CH{=}CMe\cdot CH_3} + \underset{86\%}{CH_3\cdot CH_2\cdot CMe{=}CH_2}$$

This again is orientation according to the generalised Hofmann rule, and the explanation previously illustrated applies. The fact that the ratio in which the isomeric olefins are formed is

about 6 : 1, whereas in the corresponding reaction of the dimethyl-*sec.*-butylsulphonium ion it was only about 3 : 1, is intelligible on statistical grounds alone, since the tertiary group has two shorter branches in competition with the longer branch, whilst the secondary group has only one.

Reaction rates in the tertiary series confirm control by the factors underlying the Hofmann rule. For the second-order rate-constants of the reaction

$$R{\cdot}CH_2{\cdot}CMe_2{\cdot}\overset{+}{S}Me_2 + \bar{O}Et \longrightarrow HOEt + Olefins + SMe_2$$

where R = H, Me, in 97% ethyl alcohol at 25°, with sodium ethoxide in large excess at concentrations about 0·25N, the following values [$k(E2)$ in sec.$^{-1}$ g.-mol.$^{-1}$ l.] were determined (Part XIV) :

Alk in Alk$\overset{+}{S}$Me$_2$		*tert.*-Butyl.	*tert.*-Amyl.
$10^5k(E2)$: total	longer branch	80 : 27	56 : 8
	each shorter branch	27	24

Again the higher homologue gives olefin more slowly, and nearly the whole of the diminution of velocity arises from the reduced rate of entry of the double bond into that alkyl branch which has the extra β-methyl substituent. The factor by which the β-linked methyl substituent in the *tert.*-amyl group reduces the rate of establishment of a contiguous double bond is 0·30. From the rates already given for the secondary alkyl compounds one may see that the same factor for the *sec.*-butyl group is 0·36. And from the rates for the primary compounds it follows that the factor for the *n*-propyl group is 0·45. One may reasonably conclude that just the same type of protective effect as has been assumed to arise from β-alkyl substituents in primary alkyl groups is also at work in suitably constituted secondary and tertiary alkyl groups. We interpret this effect as due to inductive electron displacement.

As compared with the secondary groups *iso*propyl and *sec.*-butyl, the two tertiary groups *tert.*-butyl and *tert.*-amyl possess an extra α-methyl substituent. The rate figures already given do not enable the effect of this α-substituent to be assessed because the temperatures are not all the same. However, at still another temperature the primary, secondary, and tertiary series have been directly compared with respect to bimolecular elimination rates, by means of the groups ethyl, *iso*propyl, and *tert.*-butyl, which respectively possess 0, 1, and 2 α-methyl substituents. For the second-order rate-constants of the reaction

$$CH_2{\cdot}CRR'{\cdot}\overset{+}{S}Me_2 + \bar{O}Et \longrightarrow HOEt + CH_2{:}CRR' + SMe_2$$

where R,R′ = H, Me, in ethyl alcohol at 45°, with sulphonium iodide and sodium ethoxide initially in concentrations 0·02 and 0·095M, respectively, the following values [$k(E2)$ in sec.$^{-1}$ g.-mol.$^{-1}$ l.] have been determined (Part XIV) :

Alk in Alk$\overset{+}{S}$Me$_2$		Ethyl.	*iso*Propyl.	*tert.*-Butyl.
$10^5k(E2)$	total	5	114	2930
	per branch	5	57	977

If, in all three cases, we consider the rate of establishment of the double bond in a given alkyl branch, then we see that, starting with ethyl, the effect of introducing the single α-methyl substituent present in the *iso*propyl group is to increase the rate by a factor of 11, whilst the effect of the second similar substituent additionally present in the *tert.*-butyl group is a further increase of the rate by a factor of 18. There can be no doubt, therefore, that the effect of an α-alkyl substituent is to accelerate bimolecular elimination, and, as we have noticed already, that is not intelligible on the basis of the simple electrostatic theory underlying the Hofmann rule.

Sectional Summary.—We here summarise our conclusions concerning bimolecular elimination from 'onium ions. Studies of orientation and reaction rate at first with ammonium and sulphonium ions containing only primary alkyl groups, and then with secondary and tertiary alkyl groups, have shown, for each of these series, that orientation corresponds to the generalised Hofmann rule, and that rate comparisons between different compounds confirm the picture of constitutional influences which follows from that rule. These orientational and kinetic phenomena satisfy in detail the requirements of Hanhart and Ingold's original interpretation of the Hofmann rule as an application of the inductive effect; and this is the dominating constitutional effect for the stated range of phenomena. However, rate comparisons between the primary, secondary, and tertiary alkyl series reveal the simultaneous operation of a constitutional effect not covered by the explanation.

(3.2) *Bimolecular Elimination in Halides : The Electromeric Effect.*—When Baker and Nathan (*J.*, 1935, 1844) first adduced evidence for the view that the electrons of a CH-bond participate in tautomeric electron-displacements, much in the manner of unshared electrons, although in general with less freedom (compare, for instance, H—C—C=C with RO—C=C), we saw immediately that this might be the internal mechanism responsible for the elimination phenomena summarised under Saytzeff's rule. However, this idea could not at once be established formally.

For in the first place, the evidence for the special form of electron displacement which Baker and Nathan had postulated, hyperconjugation, as it was subsequently called by Mulliken, Rieke, and Brown (*J. Amer. Chem. Soc.*, 1941, **63**, 41), itself required to be strengthened. That has since been done, with the result that today hyperconjugation is a well-established concept (see review * by Deasy, *Chem. Reviews*, 1945, **36**, 145).

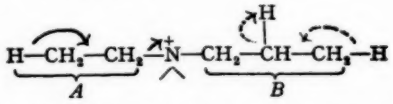
Secondly, since the whole theory, in its application to elimination, had a much wider range of consequences than was comprised within the Saytzeff rule, these more general consequences had to be tested by new experiments. This programme has now been largely fulfilled, and the record of a considerable part of it is in the preceding papers.

In the Section **3.1** we treated inductive electron-displacement as though it were the only internal mechanism; and, by restricting illustrations to a range of examples in which it was dominating, we were able to give an interpretation of orientation and reaction rate on the basis of the inductive effect alone, although the presence of a disturbing influence was noted. In a similar manner, we shall, in this Section, make the simplifying assumption that only tautomeric electron-displacements need be considered; and we shall confine illustration to a range of cases in which this effect is dominating. By following this plan we shall be able, in the first place, separately to explain and illustrate the two complementary parts of the theory in a relatively simple way. There will then remain the problem of the co-existence of the two effects, of the range over which either is dominating, and of what determines those ranges : this aspect of the matter will be discussed in Section **3.4**.

In elimination, tautomeric electron displacements originating in alkyl groups can arise only during the course of reaction : obviously there is no opportunity for Baker and Nathan's type of hyperconjugation in the initial state of a reaction of a saturated alkyl compound. Thus the internal process is one which we should classify as a polarisability effect, and we may therefore give it its specific name, the electromeric effect. Instead of considering the whole, detailed course of reaction, we may adopt the usual simplification of concentrating attention on the transition state. In this state, the electrons of a γ-CH-bond become hyperconjugated with the unsaturation electrons of the partly formed $C_\beta C_\alpha$-double bond. The hyperconjugation of these electrons modifies their wave-functions in such a way as to give them a larger share of configuration space, and therefore a smaller energy. This follows from the uncertainty principle, and is typical of those quantal effects, which are often summarised as resonance, and which at all levels of complexity, from the exchange degeneracy of a single bond onward, provide the forces of covalent combination. In our case, the result is a reduction of the energy of the transition state, and therefore of the activation energy, with a corresponding facilitation of the elimination process.

We have to extend this theory in one respect. According to Baker and Nathan's original principle, the resonance effect of an alkyl group attached to an unsaturated carbon atom would be a maximum when the alkyl group was methyl, but would diminish, and finally disappear, if it

* Note by Dr. J. W. Baker.—One statement in this review requires correction. Deasy, referring to olefin-elimination from quaternary ammonium salts, states : " Hyperconjugation, which can function as indicated at *A* but cannot function at *B* because the elimination of a negative ion cannot occur, *was assumed to be the decisive factor* " (italics new).



The argument used by Baker (*J.*, 1935, 1845) was to show why hyperconjugation was *not* operative in determining into which alkyl side-chain the double bond was introduced because " it would be ineffective in retarding cationisation of the β-hydrogen atom, which will be influenced solely by the normal inductive effect of the alkyl group attached to C_β."

This conclusion, although reached before the recognition of the significance of hyperconjugation in determining the course of all 1 : 2-eliminations which occur by the *E*1 mechanism and in neutral secondary and tertiary halides by the *E*2 mechanism, is in agreement with the findings of Professor Ingold and his collaborators in this series of papers concerning *E*2 reactions of " 'onium " compounds.

were changed successively to ethyl, *iso*propyl, and *tert.*-butyl, owing to the progressive, and finally complete loss of suitably situated CH-bonds. However, it was suggested by Hughes, Ingold, Masterman, and MacNulty (*J.*, 1940, 899) that even in the case of the *tert.*-butyl group a residual resonance effect will be found, and that in other cases a part of the total observed effect is not dependent on CH-bonds. This is because of the expectation that, when two atoms of identical nuclear charge are linked, the electrons will concentrate in the direction of the less saturated; for to do so gives them freer motions, thereby stabilising the system in accordance with the uncertainty principle. An equivalent statement is that even the electrons of saturated CC-bonds have an appreciable mobility in respect of a hyperconjugation, $C\overset{\curvearrowright}{-}C\overset{\curvearrowright}{-}C{=}C$, formally analogous to that in which the electrons of CH-bonds participate, $H\overset{\curvearrowright}{-}C\overset{\curvearrowright}{-}C{=}C$; but that such mobility in saturated CC-electrons is smaller than the analogous kind of mobility in CH-electrons. This extension of Baker and Nathan's theory is naturally quite general,* though we are here concerned only with its application to the transition state in elimination. In this application we shall for convenience use the term electromeric effect to cover both Baker and Nathan's original form of hyperconjugation and the extension described.†

In the preceding Section we considered the separate operation of the electrostatic, or inductive, effect in the bimolecular mechanism of elimination, *E*2; and we derived a set of consequences, which could be verified: included amongst them was the Hofmann rule. Just in the same way, we shall now apply the concept of the resonance, or electromeric, effect to the bimolecular mechanism, *E*2. We shall obtain a very different set of consequences, amongst which will appear the Saytzeff rule.

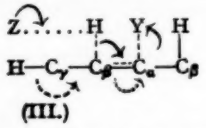
Our primary deductions from the theory of the electromeric effect may be set out under four heads. First, on account of the electromeric effect, an alkyl radical attached to the β-carbon atom of a complete alkyl group will stabilise the transition state of elimination in that group, and will therefore facilitate its degradation to an olefin. This predicted effect, which is the opposite of the action of the inductive effect, may be applied either to the relative rates of bimolecular eliminations involving different alkyl groups each in a different molecule under the same environmental conditions, or to the reactions of different alkyl groups, or of dissimilar branches of the same alkyl group, in the same molecule. Applied to primary alkyl groups, either in different molecules or in the same molecule, it means, for example, that a *n*-propyl group should give propylene more easily than an ethyl group should give ethylene; and that an *iso*butyl group should give *iso*butylene more easily still. A similar application may be made to symmetrically branched secondary and tertiary alkyl groups. Thus an *iso*propyl group should yield propylene less easily than a 3-*n*-amyl group yields pent-2-ene, and a *tert.*-butyl group should give *iso*butylene less easily than a triethylcarbinyl group gives methyldiethylethylene. If we apply our deduction differentially to the unequal branches of an unsymmetrical secondary or tertiary alkyl group, we get Saytzeff's rule. That is illustrated for the *sec.*-butyl group in formulæ (III) and (IV). Of the two possible transition states of elimination that which has a methyl radical attached to the β-end of the αβ-unsaturated bond will possess a lower-lying energy than the other, and hence the β-hydrogen atom preferentially lost on elimination will come from the most alkylated (or least hydrogenated) β-carbon atom. An alternative statement is that the preferentially formed ethylene will carry the larger number of alkyl groups, two instead of only one.

Our second main deduction is that, since either end of the developing double bond is equally available for hyperconjugation, alkyl radicals attached to the α-carbon atom of the complete

* It may be held responsible for the shortening of the central bond in 1 : 3-dienes (Jeffrey, *Proc. Roy. Soc.*, 1945, *A*, **183**, 391; 1947, *A*, **188**, 222). We suggest that, as a mechanism for securing increased overlap, the orbitals of the central bond acquire increased *p*-content from the adjacent CH-bonds, and hence change shape, shrinking longitudinally and swelling laterally in such a way as to promote overlap with the orbitals of the double bonds. One can understand thus how a bond might contract (longitudinally) without an increase of electron-content.

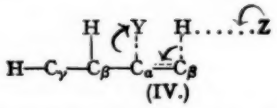
† Two extensions of Baker and Nathan's original theory have been discussed by de la Mare, Hughes, and Ingold (this vol., p. 21). They postulate hyperconjugation in the systems $C{=}C\overset{\curvearrowright}{-}C\overset{\curvearrowright}{-}Y$ and $H\overset{\curvearrowright}{-}C\overset{\curvearrowright}{-}C\overset{\curvearrowright}{-}Y$, where Y is an electron-attracting group. The first of these hyperconjugated systems, which had already been postulated by Baker (*J.*, 1939, 1155), could have importance for the transition states of elimination in special structures, *e.g.*, certain polyhalogen compounds. The second will be present in the initial states of all systems undergoing 1 : 2-elimination. The only reason why we are not compelled to take explicit account of it throughout is that it appears as an essentially constant factor in most of our comparisons.

alkyl group will exert an effect on elimination generally similar to that of alkyl radicals attached to a β-carbon atom. This will evidently be a primary effect, and it therefore provides another



(III.)

(Dotted arrows below formula denote hyperconjugation stabilising the transition state of the elimination represented by the full-line arrows above formula. Thus the *sec.*-butyl group gives 1 : 2-dimethylethylene as the main olefinic product.)



(IV.)

(There is no similarly situated γ-CH group to stabilise the transition state of this elimination, represented by the curved arrows, and hence the *sec.*-butyl group gives ethylethylene as a minor product only.)

strong contrast to the consequences of the theory of the inductive effect, according to which an α-situated radical should exert only a very small influence, owing to the distance through which electrostatic induction has to travel in order to reach the β-hydrogen atom. We can accordingly feel sure that the electromeric effect of α-alkyl radicals is the effect which will dominate in all circumstances. It follows that secondary alkyl groups should suffer bimolecular elimination more readily than primary, and tertiary more readily than secondary, provided we can assume that β-radicals, if present, are exerting comparable effects in the cases compared. Thus we should observe increasing facility of bimolecular elimination along the series ethyl, *iso*propyl, *tert.*-butyl, or along the series *n*-propyl, *sec.*-butyl, *tert.*-amyl.

The third prediction represents an extension of the first two, inasmuch as it defines the relative effects of different alkyl radicals, attached either to the β-carbon atom, or to the α-carbon atom, of the complete alkyl group. In either position, the largest effect will be exerted by the methyl radical, since it has three hydrogen atoms available for hyperconjugation. The effect will be reduced in any higher primary alkyl radical, and reduced more if a secondary alkyl radical, and still more if a tertiary alkyl radical, is substituted.

We can draw one more conclusion: for there is nothing in the theory which restricts its application to alkyl groups. We have noted how a methyl radical attached to either the β- or the α-carbon atom of the complete alkyl group, can enter into hyperconjugation with the developing double bond, thus assisting its formation. Obviously an effect of the same kind, but stronger, is to be expected if the methyl radical is replaced by an unsaturated, and therefore properly conjugated, radical such as vinyl or phenyl. The theory of the electromeric effect on elimination is, indeed, general for unsaturated and pseudo-unsaturated substituents.

Just as in the preceding Section we found the predictions of the theory of the inductive effect to be much broader than the empirical rule of Hofmann, which they included, so now we notice that the theory of the electromeric effect has a much greater range of verifiable consequences than those empirically recognised in the rule of Saytzeff. Numerous observations in the older literature of eliminations are consistently accommodated by this broader theory; but we have thought it desirable to subject its predictions to the more severe test of reaction kinetics, and it was with that object that much of the work described in the preceding papers was carried out. We shall now illustrate the above-mentioned consequences of the theory of the electromeric effect by reference to bimolecular eliminations from alkyl bromides.

The effect of β-substituents in primary alkyl groups is shown by the following second-order rate-constants [$k(E2)$ in sec.$^{-1}$ g.-mol.$^{-1}$ l.], applying to the reactions

$$R{\cdot}CH_2{\cdot}CH_2Br + \bar{O}Et \longrightarrow HOEt + R{\cdot}CH{:}CH_2 + \bar{B}r$$

$$R_2CH{\cdot}CH_2Br + \bar{O}Et \longrightarrow HOEt + R_2C{:}CH_2 + \bar{B}r$$

where R = H, Me, Et, *n*-Pr, and Ph, in ethyl alcohol, at 55°, with total salt concentrations of about 0·1M (Hughes, Ingold, Masterman, and MacNulty, *loc. cit.*; and Part IX):

Group	Ethyl.	*n*-Propyl.	*n*-Butyl.	*n*-Amyl.	*iso*Butyl.	2-Phenylethyl.
R or R_2	H	Me	Et	*n*-Pr	Me_2	C_6H_5
$10^5k(E2)$	1·6	5·3	4·3	3·5	8·5	561

We see that a single β-methyl substituent increases the bimolecular rate of elimination, that two β-methyl substituents increases it more, and that a single β-phenyl substituent does so very strongly; and we notice that higher alkyl β-substituents also increase the rate, but not so strongly as methyl does. These relationships are probably quite general, for we can illustrate

some of them by means of rate constants [$k(E2)$ in sec.$^{-1}$ g.-mol.$^{-1}$ l.] applying to secondary and tertiary alkyl groups. Thus for the secondary halide reactions

$$R{\cdot}CH_2{\cdot}CHMeBr + \bar{O}Et \longrightarrow HOEt + R{\cdot}CH{:}CHMe + \bar{B}r$$

where R = H, Me, and Et, in ethyl alcohol, at 25°, with a total salt concentration of about 1·0M, we find the following second-order rate-constants (Part X) :

Group	*iso*Propyl.	*sec.*-Butyl.	2-*n*-Amyl.
R	H	Me	Et
$10^5k(E2)$	0·118	0·282	0·196

For the secondary halide reactions

$$R{\cdot}CH_2{\cdot}CHEtBr + \bar{O}Et \longrightarrow HOEt + R{\cdot}CH{:}CHEt + \bar{B}r$$

where R = H and Me, under the same conditions as before, the following second-order rate-constants have been found (Part X) :

Group	*sec.*-Butyl.	3-*n*-Amyl.
R	H	Me
$10^5k(E2)$	0·065	0·200

Finally, for the tertiary halide reactions

$$R{\cdot}CH_2{\cdot}CMe_2Br + \bar{O}Et \longrightarrow HOEt + R{\cdot}CH{:}CMe_2 + \bar{B}r$$

where R = H and Me, still under the same conditions, we have the following second-order constants (Part XI) :

Group	*tert.*-Butyl.	*tert.*-Amyl.
R	H	Me
$10^5k(E2)$	1·00	4·20

The effect of α-substituents on the bimolecular elimination rates of alkyl bromides seems to be equally regular, as may be illustrated by some further rate constants [$k(E2)$ in sec.$^{-1}$ g.-mol.$^{-1}$ l.]. The following second-order constants relate to the reactions

$$CH_3{\cdot}CHRBr + \bar{O}Et \longrightarrow HOEt + CH_2{:}CHR + \bar{B}r$$

$$CH_3{\cdot}CR_2Br + \bar{O}Et \longrightarrow HOEt + CH_2{:}CR_2 + \bar{B}r$$

where R = H, Me, Et, *n*-Pr, and Ph, in ethyl alcohol, at 25°, with a total salt concentration of about 1·0M (Parts X and XI; the figures for ethyl and 1-phenylethyl are estimated from measured rates under other conditions—cf. Hughes, Ingold, Masterman, and MacNulty, *loc. cit.*) :

Group	Ethyl.	*iso*Propyl.	*sec.*-Butyl.	3-*n*-Amyl.	*tert.*-Butyl.	*tert.*-Amyl.	1-Phenylethyl.
R or R_2	H	Me	Et	*n*-Pr	Me_2	MeEt	C_6H_5
$10^5k(E2)$	0·025	0·118	0·065	0·080	1·00	0·85	0·79

We notice that a single α-methyl substituent increases the second-order rate-constant, and that two α-methyl substituents do so more strongly, as also does a single α-phenyl substituent; and again we find that, although higher alkyl substituents increase the rate, they do so less strongly than methyl does. Some of the same relationships can be illustrated for the reactions

$$CH_3{\cdot}CH_2{\cdot}CHRBr + \bar{O}Et \longrightarrow HOEt + CH_3{\cdot}CH{:}CHR + \bar{B}r$$

$$CH_3{\cdot}CH_2{\cdot}CR_2Br + \bar{O}Et \longrightarrow HOEt + CH_3{\cdot}CH{:}CR_2 + \bar{B}r$$

in which an extra β-linked methyl substituent is present, and R = H, Me, and Et. Under the same conditions as before, the second-order rate-constants are as follows (Parts X and XI; the figure for *n*-propyl is estimated from measured rates under other conditions—cf. Part IX, and also ref. 31 of Section 1.1) :

Group	*n*-Propyl.	*sec.*-Butyl.	3-*n*-Amyl.	*tert.*-Amyl.
R or R_2	H	Me	Et	Me_2
$10^5k(E2)$	0·083	0·282	0·200	4·20

It is interesting to notice that the methyl radical exerts a larger effect from the α-position, whilst the phenyl radical acts more strongly from the β-position. This may possibly be a result

of the simultaneous presence of the electrostatic effect, which becomes important in the case of β-linked substituents, and for β-methyl (inductive electron-repulsion) opposes the resonance effect, but for β-phenyl supports it (electron attraction due to the Ar–C bond dipole).

The manner in which the above-described effects on bimolecular elimination rate combine together to produce orientational effects in secondary and tertiary alkyl halides can be understood from Table I. There the second-order rate-constants for elimination under a uniform set of conditions are given in the form of the partial rates which correspond to elimination along the different branches of the alkyl groups. These partial rates are entered against the associated alkyl branches on either side of the chemical formulæ, and adjacent to each rate figure is a note of the substituents attached to the α- and β-ends of the double bond formed, the labels α- and β- denoting, as usual, those carbon atoms from which the halogen and hydrogen atoms, respectively, are lost in the formation of the double bond.

TABLE I.

Itemised Second-order Rate-constants of Elimination, arranged to show the Manner in which they determine Orientation, in the Bimolecular Eliminations of Alkyl Halides.

Reactions of alkyl bromides with *ca.* 1N-sodium ethoxide in dry ethyl alcohol at 25°. Second-order rate-constants, $k(E2)$, in sec^{-1}. g.-$mol.^{-1}$ l. Notation for showing positions of substituents:

$$\overset{\beta}{C}=\overset{\alpha}{C}-CH \longleftarrow \overset{\beta}{C}H-\overset{\alpha}{C}Br-CH \longrightarrow CH-\overset{\alpha}{C}=\overset{\beta}{C}$$

No.	Substituents. β.	Substituents. α.	$10^5k(E2)$ per branch.	Alkyl halide.	$10^5k(E2)$ per branch.	Substituents. α.	Substituents. β.
1	—	Me	0·118	$CH_3{\cdot}CHBr{\cdot}CH_3$	0·118	Me	—
2	Me	Me	0·282	$CH_3{\cdot}CH_2{\cdot}CHBr{\cdot}CH_3$	0·065	Et	—
3	Et	Me	0·196	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHBr{\cdot}CH_3$	0·080	*n*-Pr	—
4	Me	Et	0·200	$CH_3{\cdot}CH_2{\cdot}CHBr{\cdot}CH_2{\cdot}CH_3$	0·200	Et	Me
5	—	Me_2	1·00	$CH_3{\cdot}CBr(CH_3)_2$	1·00	Me_2	—
					1·00	Me_2	—
6	Me	Me_2	4·20	$CH_3{\cdot}CH_2{\cdot}CBr(CH_3)_2$	0·85	MeEt	—
					0·85	MeEt	—

Comparing entries 1 and 2, one sees (left-hand columns) that, in agreement with theory, the extra β-Me in example 2 accelerates the formation of but-2-ene as compared with its lower homologue, whereas (right-hand columns) the replacement of α-Me by α-Et retards, as it should, the formation of but-1-ene. Both rate changes contribute to the production of a considerable orienting effect according to Saytzeff's rule (Part X):

$$(81\%)\ CH_3{\cdot}CH{:}CH{\cdot}CH_3 \xleftarrow[E2]{} CH_3{\cdot}CH_2{\cdot}CHBr{\cdot}CH_3 \xrightarrow[E2]{} CH_3{\cdot}CH_2{\cdot}CH{:}CH_2\ (19\%)$$

Comparing entries 2 and 3, we find (left), again in agreement with theory, that the replacement of β-Me by β-Et retards the formation of pent-2-ene in comparison with but-2-ene, whereas (right) the replacement of α-Et by α-Pr, which in theory should have but little effect, actually slightly accelerates the formation of pent-1-ene in comparison with but-1-ene. The result is still an orientation according to the Saytzeff rule; but it is a weaker orientation in the case of the pentenes than in that of the butenes, contrary to what might naïvely have been assumed in view of the greater dissymmetry of the 2-*n*-amyl than of the 2-*n*-butyl radical (Part XI):

$$(71\%)\ CH_3{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_3 \xleftarrow[E2]{} CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHBr{\cdot}CH_3 \xrightarrow[E2]{} CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CH_2\ (29\%)$$

In such a manner does the theory accommodate a number of fine details, which are not expressed in any empirical rule.

If we compare examples 4 and 3 in Table I, we see (left) that an interchange of the substituents Me and Et between the α- and β-positions has scarcely any effect on the rate of establishment of the double bond in the left-hand alkyl branch. This is in no way surprising. The whole of the orienting effect which is introduced on passing from symmetric 3-*n*-amyl bromide to asymmetric 2-*n*-amyl bromide is due to the decreased ease of establishment of the double bond in the right-hand alkyl branch. As to this, although two groups become changed (see Table I, right), most of the effect is doubtless due to the loss of the β-Me substituent.

Examples 5 and 6 of Table I show (left) that the extra β-Me group in the left-hand branch of the *tert.*-amyl bromide molecule accelerates the formation of a double bond in that direction, as it should according to our theory. But it is also apparent (right) that the same structural change amounts to a replacement of α-Me by α-Et with respect to the establishment of the double bond in either of the right-hand branches of the molecule. Hence the alteration should have a retarding effect on those processes, as in fact it has. The orientational proportions are a resultant of these two effects, together with that of the doubled statistical weight of the terminally unsaturated, with respect to the non-terminally saturated, olefin (Part XI) :

$$(71\%)\ CH_3{\cdot}CH{:}C(CH_3)_2 \xleftarrow[E2]{} CH_3{\cdot}CH_2{\cdot}CBr(CH_3)_2 \xrightarrow[E2]{} CH_3{\cdot}CH_2{\cdot}C(CH_3){:}CH_2\ (29\%)$$

Reference may be made to the orientational result represented in the following scheme (Part XV) :

$$(82\%)\ (CH_3)_2C{:}CH{\cdot}CH_3 \xleftarrow[E2]{} (CH_3)_2CH{\cdot}CHI{\cdot}CH_3 \xrightarrow[E2]{} (CH_3)_2CH{\cdot}CH{:}CH_2\ (18\%)$$

No rates have been measured for this case, but we should expect the extra methyl substituent which is here present, over and above those which appear in example 2 of Table I, to increase the rate of formation of the non-terminally unsaturated olefin, and, essentially for this reason, to lead to the still more decided orientation of the observed Saytzeff type.

This is a convenient place in which to refer to the differential influence of alkyl structure on elimination and substitution in the second-order reactions of alkyl halides, and to the consequential effect on the proportion of olefin formed. Considering first the successive introduction of α-linked methyl substituents, we know that in the series ethyl, *iso*propyl, *tert.*-butyl, the rate of bimolecular substitution decreases (Ref. 31 of Section 1.1; Dostrovsky, Hughes, and Ingold, *J.*, 1946, 157); and we have seen above that the rate of bimolecular elimination increases; therefore the proportion of olefin, $E2/(S_N2 + E2)$, must increase strongly. The following rate-constants [$k(S_N2)$ and $k(E2)$ in sec.$^{-1}$ g.-mol.$^{-1}$ l.], and olefin proportions, for the bimolecular reactions of the alkyl bromides with sodium ethoxide (1N or more) in ethyl alcohol at 55°, illustrate this :

	Ethyl.	*iso*Propyl.	*tert.*-Butyl.
$10^5k(S_N2)$	118	2·1	small
$10^5k(E2)$	1·2	7·6	50
Proportion of olefin, %	1·0	79	~100

With regard to successively introduced β-linked methyl radicals, we know that in the series ethyl, *n*-propyl, *iso*butyl, the rate of bimolecular substitution falls, though not so strongly as before; and we have noticed above that the rate of bimolecular elimination rises, but again less markedly than in the previous series; therefore the proportion of olefin will exhibit an increase, which, however, will be less pronounced than that produced by α-linked methyl radicals. In illustration, the following rate constants and olefin proportions may be quoted, which refer to the bimolecular reactions of the alkyl bromides with sodium ethoxide (about 0·1N) in ethyl alcohol at 55° :

	Ethyl.	*n*-Propyl.	*iso*Butyl.
$10^5k(S_N2)$	172	55	5·8
$10^5k(E2)$	1·6	5·3	8·5
Proportion of olefin, %	0·9	8·9	60

Different relations will naturally obtain for the bimolecular reactions of 'onium salts, whose eliminations are controlled largely by the inductive, rather than by the electromeric, effect. However, we have insufficient data on bimolecular substitution rates in 'onium salts for the purposes of a general discussion, the difficulty being that the presence of several different groups in most of the 'onium salts whose decompositions have been kinetically studied usually makes the substitution process composite and tedious to analyse.

Sectional Summary.—We now summarise the general results of our study of rate and orientation in the bimolecular eliminations of alkyl halides. In these reactions the general rule is that the formation of a double bond in any given position is accelerated by an alkyl radical at either end of it, the most effective alkyl radical being methyl, although phenyl is considerably more effective than any simple alkyl radical. On this basis, one can understand the variation with structure of the rates of bimolecular elimination in a large variety of primary, secondary, and tertiary alkyl halides; and also the orientational data for dissymmetrically branched secondary and tertiary alkyl halides. The orientational results all conform to the qualitative, empirical rule of Saytzeff; but they also disclose quantitative variations, which agree in detail

with the more general rule stated above. All these effects of structure on reaction rate and orientation are rendered intelligible by the proposed theory of the electromeric effect, which consists in the assumption of a hyperconjugation or conjugation operating between the developing double bond and the radicals adjacent to it, in the transition state of reaction. This appears as the controlling influence; but certain detailed results, such as the dissimilar changes in the effectiveness of a methyl radical and of a phenyl radical when shifted from one end of the double bond to the other, point to the presence of a disturbance, which can plausibly be identified as the inductive effect.

Not only do alkyl groups at either end of a developing double bond increase the rate of its formation in these bimolecular reactions of alkyl halides: they also decrease the rate of the concomitant bimolecular substitutions. Therefore they increase largely the proportion in which olefins are formed in the total bimolecular decomposition.

(3.3) *Unimolecular Elimination in Halides and Sulphonium Salts: The Electromeric Effect.*— Unimolecular elimination has been observed with secondary and tertiary alkyl halides, and secondary and tertiary alkylsulphonium ions: it has not yet been realised (except in association with molecular rearrangement) for primary alkyl halides, or for 'onium ions containing only primary alkyl groups.

All our evidence concerning the orientation of unimolecular elimination, whether of alkyl halides or of alkylsulphonium salts, points to the conclusion that the controlling influence is the electromeric effect. In particular, orientation follows the Saytzeff rule. It is, of course, not remarkable that the unimolecular eliminations of halides and of sulphonium salts should behave similarly in this respect, even though the bimolecular eliminations of halides and of sulphonium salts behave very differently; for orientation in unimolecular elimination is a property of the carbonium ion, which is an intermediate of that mechanism, and the carbonium ion corresponding to a given alkyl group is the same, whether it comes from an alkyl halide or an alkylsulphonium ion. Qualitatively then, orientation in unimolecular elimination, either of halides or of sulphonium ions, resembles orientation in the bimolecular eliminations of alkyl halides. But we shall find that orientation in the unimolecular reactions is quantitatively more extreme than in the bimolecular reactions of halides.

Because of the two-stage nature of the unimolecular mechanism, the rate constant of elimination, $k(E1)$, is composite, and this has to be borne in mind when using it for the purpose of assessing constitutional effects. It is the product of the rate of heterolysis, and the fraction of the formed carbonium ion which completes an elimination. From some points of view this fraction, that is, the percentage of olefin formed in the unimolecular reaction, is more simply related to structure than is the rate of the separate process of elimination. Some secondary alkyl bromides are compared below with respect to the percentage of olefin which they yield in " 60% " aqueous ethyl alcohol at 80° (Part X):

R in RBr	$CH_3 \diagdown \atop CH_3 \diagup CH$	$CH_3 \cdot CH_2 \diagdown \atop CH_3 \diagup CH$	$CH_3 \cdot CH_2 \diagdown \atop CH_3 \cdot CH_2 \diagup CH$	$CH_3 \cdot CH_2 \cdot CH_2 \diagdown \atop CH_3 \diagup CH$
Proportion of olefin, %	4·6	8·5	15·1	6·8
$10^5 k(E1)$	0·32	0·63	0·90	0·38

The rate constants for elimination [$k(E1)$ in sec.$^{-1}$] are seen to show much the same trend as the olefin proportion. Even though data are not available which would permit the figures for the two unsymmetrical compounds to be split up into parts corresponding to reaction in the alternative branches of the alkyl group, it is clear from the results that a β-linked methyl substituent facilitates the completion of an elimination, and that a β-linked ethyl substituent does the same, but not so strongly. What we have not proved is that these effects are localised in the alkyl branch to which the substituent is attached; but it would be reasonable to assume that they are so localised: the whole picture then agrees perfectly with control by the electromeric effect.

Orientational data, such as are lacking for the unimolecular eliminations of the asymmetric secondary alkyl halides, are available for one such secondary alkylsulphonium ion (Part XV):

$$(CH_3)_2CH \diagdown \atop CH_3 \diagup CH \cdot \overset{+}{S}Me_2 \longrightarrow (CH_3)_2C \diagdown \atop CH_3 \diagup CH\ (91\%) + (CH_3)_2CH \diagdown \atop CH_2 \diagup CH\ (9\%)$$

These figures express strong orientation according to Saytzeff's rule, stronger than for the already mentioned bimolecular reaction of the corresponding alkyl iodide. This again corresponds to control by the electromeric effect. The proportion of total olefin was 7%, a figure which is of the same order of magnitude as those obtained for the corresponding reactions of the secondary

alkyl bromides, though precise comparison is not possible, because the solvent and temperature were not the same as for the bromides.

A comparison of the proportions in which olefins are formed in the first-order reactions of *iso*propyl and *tert.*-butyl halides or sulphonium ions, or alternatively in the first-order decompositions of *sec.*-butyl and *tert.*-amyl halides or sulphonium ions, shows that an α-linked methyl substituent in the alkyl chain is even more effective than a β-linked methyl substituent in directing the completion of the process towards elimination. Actually, the figures available to illustrate this do not apply to identical conditions of solvent and temperature; but, as the following list shows, the differences in olefin proportion are so large that there can be no doubt about the qualitative conclusion (Parts VI, VII, VIII, and X):

*iso*Propyl bromide	in 60% aq. EtOH	at 80°	yields	4·6%	olefin
tert.-Butyl chloride	in 80% "	65°	"	36·3%	"
$But^{+}SMe_2$	in 80% "	65°	"	35·7%	"
sec.-Butyl bromide	in 60% aq. EtOH	at 80°	yields	8·5%	olefin
tert.-Amyl chloride	in 80% "	50°	"	40·3%	"
$Am^{t}\overset{+}{S}Me_2$	in 60% "	65°	"	39·8%	"
"	in 80% "	65°	"	49·4%	"
"	in 80% "	83°	"	53·4%	"

A detailed analysis of the manner in which the rates and proportions of unimolecular elimination along the different branches of a dissymmetric alkyl group contribute to the effect of a structural change on the overall elimination rate, the overall olefin proportion, and the orientation of elimination can be offered in the form of a comparison either of the unimolecular reactions of *tert.*-butyl and *tert.*-amyl bromides, or of those of dimethyl-*tert.*-butyl- and -*tert.*-amyl-sulphonium ions. We here employ the former example (Part XI), partly because it permits an instructive comparison of bimolecular and unimolecular eliminations of the same substances, all fundamentally under the control of the electromeric effect, and partly because we shall be using the latter example in another connexion presently.

The analysis is given in the upper part of Table II. These figures may be compared with those of the similar analysis which is given for the bimolecular reactions in entries 5 and 6 of Table I. The corresponding data on the left of either table show a qualitatively similar structural influence: the extra β-Me substituent in the amyl compound facilitates the establishment of the double bond in the alkyl branch to which it belongs. But the effect is larger for the unimolecular than for the bimolecular mechanism. All this is true, whether we think of the rate at which, or the proportion in which, the double bond is established in the appropriate part of the molecule. However, the figures on the right of the two tables reveal a certain difference: the replacement of α-Me_2 by α-MeEt, which in the bimolecular reaction, consistently with the theory of control by the electromeric effect, reduced the rate of introduction of the double bond into those alkyl branches with respect to which the indicated radicals are α-substituents, is now found to accelerate the same process in the unimolecular reaction. This, however, is not an anomaly: it is immediately explained by the mechanistic difference. The rate-constant $k(E1)$ contains, as a factor, the rate of ionisation of the alkyl halide, and this is greater for *tert.*-amyl than for *tert.*-butyl bromide. We avoid this irrelevant consideration if we pay attention to olefin proportions rather than to rates; and then we find that, in the completion of unimolecular elimination, the replacement of α-Me_2 by α-MeEt reduces, as it should if the control is by the electromeric effect, the extent to which the double bond is established in those alkyl branches with respect to which these radicals are α-substituents. The way in which these itemised rates and proportions combine to produce overall results is indicated in the lower part of Table II. The orientations is again of the Saytzeff type; and it is more extreme than that of the corresponding bimolecular reaction (Section 3.2).

A closely similar discussion could be given of the reaction rates, olefin proportions, and orientation of unimolecular elimination in dimethyl-*tert.*-butyl- and -*tert.*-amyl-sulphonium salts, the data for which are summarised in Table III (p. 2112).

Up to this point the discussion of the present Section has been concerned with the proportions in which a total unimolecular reaction, having passed through the preliminary, slow heterolysis, will pursue the various final, rapid stages open to it, thus producing a substitution product as well as one or more olefins. We have still to deal with the effect of structure on the common preliminary heterolysis, and particularly with the question of whether the inductive or the electromeric effect principally controls the rate of this process in simple alkyl compounds. We can assume that sufficiently polar substituents will give control to the inductive, and

TABLE II.

Itemised First-order Rates of Elimination and Proportions of Olefin, arranged to show the Manner in which they determine Overall Results, in Unimolecular Eliminations of Alkyl Halides.

Reactions of alkyl bromides in ethyl alcohol at 25°. First-order rate-constants, k_1 and $k(E1)$, in sec.$^{-1}$. Notation for showing the positions of substituents:

$$\overset{\beta\ \alpha}{C{=}C{-}CH} \longleftarrow \overset{\alpha\qquad\beta}{CH{-}CBr{-}CH} \longrightarrow \overset{\alpha\ \beta}{CH{-}C{=}C}$$

Substituents. β.	Substituents. α.	Per branch. % Olefin.	Per branch. $10^5k(E1)$.	Alkyl halide.	Per branch. $10^5k(E1)$.	Per branch. % Olefin.	Substituents. α.	Substituents. β.
—	Me_2	6·3	0·029	$CH_3{\cdot}CBr<^{CH_3}_{CH_3}$	0·029	6·3	Me_2	—
					0·029	6·3	Me_2	—
Me	Me_2	29·6	0·323	$CH_3{\cdot}CH_2{\cdot}CBr<^{CH_3}_{CH_3}$	0·036	3·3	MeEt	—
					0·036	3·3	MeEt	—

Overall Rates and Olefin Proportions:

	10^5k_1.	$10^5k(E1)$.	% Olefin.
tert.-Butyl	0·45	0·086	19·0
tert.-Amyl	1·09	0·395	36·3

Overall Orientation:

	$CH_3{\cdot}CH{:}C(CH_3)_2$.	$CH_3{\cdot}CH_2{\cdot}C(CH_3){:}CH_2$.
tert.-Amyl, %	82	18

sufficiently unsaturated substituents to the electromeric effect; but alkyl groups present a special problem since they are neither strongly polar nor strongly unsaturated. We shall neglect the steric effect, since, as has been pointed out before, it is seldom important in unimolecular reactions (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 620; Day and Ingold, *ibid.*, p. 699; Dostrovsky, Hughes, and Ingold, *J.*, 1946, 190).

It is useful to refer to examples which show the effect of structure on rates of heterolysis in the aralphyl series; for the present a contrast with the corresponding reactions of simple alkyl compounds. The following relative unimolecular rates have been recorded for the heterolysis of *p*-methyl- and *p*-ethyl-benzhydryl chloride in " 80% " aqueous acetone at 0° (Hughes, Ingold, and Taher, *J.*, 1940, 949):

$$H{-}CH_2{\cdot}C_6H_4{\cdot}CHPhCl\ (\text{rate} = 1) \qquad CH_3{-}CH_2{\cdot}C_6H_4{\cdot}CHPhCl\ (\text{rate} = 0{\cdot}75)$$

The ethyl compound thus exhibits the lower rate (and the larger Arrhenius activation energy—*loc. cit.*), and this at once shows that the differential electromeric effect outweighs the differential inductive effect in these cases. We can conclude that the electromeric effect is important here, having, no doubt, been enhanced by the unsaturation of the p-C_6H_4 system. In the purely aliphatic series the situation is different. For the heterolysis rates of *tert.*-butyl and *tert.*-amyl bromides in ethyl alcohol at 25°, we find (Table II) the following relationship:

$$H{-}CH_2{\cdot}CHMe_2Br\ (\text{rate} = 1) \qquad CH_3{-}CH_2{\cdot}CMe_2Br\ (\text{rate} = 2{\cdot}42)$$

Obviously the differential inductive effect now predominates: we can certainly conclude that the inductive effect is important, more so, relatively to the electromeric effect, than in the aralphyl series. On the other hand, when we replace the bromine atom in these examples by the more strongly electron-attracting sulphonium pole, then the increase of rate arising from the replacement of methyl by ethyl becomes more marked, as is shown by the following data (Table III) for the relative rates of heterolysis of dimethyl-*tert.*-butyl- and -*tert.*-amyl-sulphonium ions in ethyl alcohol at 50°:

$$H{-}CH_2{\cdot}CMe_2{\cdot}\overset{+}{S}Me_2\ (\text{rate} = 1) \qquad CH_3{-}CH_2{\cdot}CMe_2{\cdot}\overset{+}{S}Me_2\ (\text{rate} = 8{\cdot}40)$$

In these cases it seems a safe conclusion that the inductive effect is the dominating polar factor.

Sectional Summary.—We here summarise the results of our study of unimolecular elimination. For both alkyl halides and alkylsulphonium ions, the general rule has been established that the proportion in which the total unimolecular reaction is completed by a route which involves the introduction of a double bond between a given pair of carbon atoms is increased by the attachment of a methyl or ethyl substituent to either of those carbon atoms; and the increase produced

by a methyl radical is greater than that produced by an ethyl radical. A considerable variety of experimental results can be referred to this rule, which includes the Saytzeff rule but is much more general: they relate to the proportions in which olefins are formed in the unimolecular reactions of secondary alkyl halides, the orientation ratio for unimolecular olefin formation from a secondary alkylsulphonium ion, and the greater proportions of olefin obtained in unimolecular reactions from tertiary than from secondary alkyl halides, and from tertiary than from secondary alkylsulphonium ions; and they include also the detailed analyses which have been made of the unimolecular rate, olefin proportions, and orientation ratios, for a pair of tertiary alkyl bromides, and again, for a pair of tertiary alkylsulphonium ions. Orientation is according to the Saytzeff rule, but is more extreme than that found for the bimolecular reactions of alkyl halides. The theoretical significance of all this is recognised to be dominating control of the final, rapid stage of unimolecular elimination by the electromeric effect.

In general, the heterolysis, which constitutes the initial slow stage of unimolecular reactions, is controlled jointly by the inductive and electromeric effects; but for simple alkyl compounds the inductive effect has a special importance, which is greater for sulphonium ions than for halides. (We may expect it to be greater still for ammonium ions, but this has not yet been verified.)

(3.4) *Co-existence of the Inductive and Tautomeric Effects.*—Originally, the Hofmann rule was applied to elimination from primary alkyl groups in ammonium ions, and the Saytzeff rule to elimination from secondary and tertiary alkyl groups in alkyl halides; and both rules were applied without reference to the kinetics of the elimination process. We have been concerned to discover what exactly bounds the separate fields of application of the two rules—whether it be the chemical nature of the original molecule ('onium salt or halide), or the type of the alkyl group (primary, secondary, or tertiary), or the mechanism of elimination (bimolecular or unimolecular). We now know that for alkyl compounds the determining circumstances are a combination of the first and third of these factors, the separate ranges being as follows: (i) bimolecular eliminations from alkyl groups in ammonium and sulphonium salts and in sulphones follow the Hofmann rule; (ii) bimolecular eliminations from alkyl halides follow the Saytzeff rule; and (iii) all unimolecular eliminations, whether of alkyl-'onium ions or alkyl halides, follow the Saytzeff rule. As we have seen, the Hofmann rule signalises control by the inductive effect, and the Saytzeff rule control by the electromeric effect.

The remarkable change which takes place in the influence of structure on the reaction rates which collectively determine orientation, when we cross the boundary between the regions of control by the two rules may be illustrated by reference to Tables III and IV. We are dealing here with identically the same structures, the dimethyl-*tert.*-butyl- and -*tert.*-amyl-sulphonium ions. From Table III to Table IV we cross the boundary between the domains of the two rules merely by changing from one kinetic form of elimination to the other.

In Table III we give both the rates and olefin proportions for elimination in the various alternative directions, in order to allow comparison with Table IV. But since Table III refers to the bimolecular mechanism, it is here the rates, rather than the olefin proportions, which have the simpler relation to structure. The extra β-linked methyl substituent decreases the rate of elimination in the long branch of the *tert.*-amyl group, in accordance with the conclusion that the inductive effect is dominant. The rate of elimination in the shorter branches, which should have been substantially reduced, owing to the replacement of a methyl substituent by ethyl, if the electromeric effect had been in control, is only slightly altered; and it should be altered hardly at all by the inductive effect, because the structural change is too remote from the β-hydrogen atom to affect it appreciably by the electrostatic mechanism. The small observed rate difference could, of course, be due to a weak underlying electromeric effect: if it were present, that certainly is how it would show itself. The resultant effect of all these individual rate changes on overall rate and orientation is shown in the lower part of Table III.

In Table IV both rates and olefin proportions are again given, but since the data refer to the unimolecular mechanism, it is now the olefin proportions, rather than the rates, which are the more simply related to structure (cf. Section 3.3). We find that the extra β-methyl substituent increases the proportion of elimination in the long branch of the *tert.*-amyl group, and reduces the proportion in the shorter branches, both in accordance with a controlling electromeric effect. In the overall results of these changes (Table IV, bottom), we find a reversal in the direction of every one of the structural effects which were found to arise in bimolecular elimination (Table III, bottom).

Another crossing of the boundary between the domains of the Hofmann and Saytzeff rules is made if we pass from the data of Table III to those in Table I, entries 5 and 6. In this case we do not change the mechanism, which is bimolecular (*E*2), but we do change the electron-

TABLE III.

Itemised Second-order Rate-constants of Elimination, arranged to show how they determine Orientation in Bimolecular Eliminations of Alkylsulphonium Salts.

Reactions of sulphonium ethoxides in " 97% " ethyl alcohol at 24°. Second-order constants k_2 and $k(E2)$ in sec.$^{-1}$ g.-mol.$^{-1}$ l. Notation for positions of substituents:

$$\overset{\beta}{C}=\overset{\alpha}{C}-CH \longleftarrow \overset{\beta}{C}H-\overset{\alpha}{C}(\overset{+}{S}Me_2)-\overset{\beta}{C}H \longrightarrow CH-\overset{\alpha}{C}=\overset{\beta}{C}$$

Substituents. β.	Substituents. α.	Per branch. % Olefin.	Per branch. $10^5k(E2)$.	Sulphonium ion.	Per branch. $10^5k(E2)$.	Per branch. % Olefin.	Substituents. α.	Substituents. β.
—	Me_2	33	27	$CH_3{\cdot}C(\overset{+}{S}Me_2)<^{CH_3}_{CH_3}$	27	33	Me_2	—
					27	33	Me_2	—
Me	Me_2	14	8	$CH_3{\cdot}CH_2{\cdot}C(\overset{+}{S}Me_2)<^{CH_3}_{CH_3}$	24	41	MeEt	—
					24	41	MeEt	—

Overall Rates and Olefin Proportions:

	10^5k_2.	$10^5k(E2)$.	% Olefin.
tert.-Butyl	80	80	100
tert.-Amyl	58	56	96

Overall Orientation:

	$CH_3{\cdot}CH{:}C(CH_3)_2$.	$CH_3{\cdot}CH_2{\cdot}C(CH_3){:}CH_2$.
tert.-Amyl, %	14	86

TABLE IV.

Itemised First-order Rates and Proportions of Elimination, arranged to show how they determine Overall Results in Unimolecular Eliminations of Alkylsulphonium Salts.

Reactions of sulphonium iodides in " 97% " ethyl alcohol at 50°. First-order constants, k_1 and $k(E1)$, in sec.$^{-1}$. Notation for positions of substituents:

$$\overset{\beta}{C}=\overset{\alpha}{C}-CH \longleftarrow \overset{\beta}{C}H-\overset{\alpha}{C}(\overset{+}{S}Me_2)-\overset{\beta}{C}H \longrightarrow CH-\overset{\alpha}{C}=\overset{\beta}{C}$$

Substituents. β.	Substituents. α.	Per branch. % Olefin.	Per branch. $10^5k(E1)$.	Sulphonium ion.	Per branch. $10^5k(E1)$.	Per branch. % Olefin.	Substituents. α.	Substituents. β.
—	Me_2	17	0·30	$CH_3{\cdot}C(\overset{+}{S}Me_2)<^{CH_3}_{CH_3}$	0·30	17	Me_2	—
					0·30	17	Me_2	—
Me	Me_2	56	8·41	$CH_3{\cdot}CH_2{\cdot}C(\overset{+}{S}Me_2)<^{CH_3}_{CH_3}$	0·63	4	MeEt	—
					0·63	4	MeEt	—

Overall Rates and Olefin Proportions:

	10^5k_1.	$10^5k(E1)$.	% Olefin.
tert.-Butyl	1·8	0·9	51
tert.-Amyl	15·0	9·7	64

Overall Orientation:

	$CH_3{\cdot}CH{:}C(CH_3)_2$.	$CH_3{\cdot}CH_2{\cdot}C(CH_3){:}CH_2$.
tert.-Amyl, %	87	13

attracting group from a sulphonium pole (control by the Hofmann rule) to a halogen atom (control by the Saytzeff rule). The strong contrast of constitutional influences, which here again arises, becomes smoothed away, if we make the same change in the electron-attracting group, but now consider the unimolecular mechanism ($E1$) (control by the Saytzeff rule in both types of compound), as we may do by passing from the data of Table IV to those of Table II. The structural effects on the olefin rates shown in Table I are qualitatively similar to the effects on the olefin proportions given in Tables II and IV, as is consistent with the theory that the same type of orientational control, *viz.*, the electromeric effect, is operating on different mechanisms.

There are a number of elimination reactions which have not yet been investigated kinetically with respect to mechanism, but which have been studied in a preparative way sufficiently to

disclose the predominating form of orientation. Guided by our more detailed knowledge of the reactions of ammonium and sulphonium ions, sulphones, and halides, we can use such orientational observations in order to make plausible suggestions concerning mechanism. As examples, we may consider the homogeneous dehydration of alcohols (*a*) in the presence of acids, (*b*) by the action of iodine (Hibbert's reaction). Both these reactions are known to obey Saytzeff's rule (Whitmore and Evers, *J. Amer. Chem. Soc.*, **1933**, **55**, 812; Whitmore and Rothrock, *ibid.*, p. 1106; Church, Whitmore, and McGrew, *ibid.*, p. 1528; Thompson and Sherrill, *ibid.*, **1936**, **58**, 745). For reaction (*b*), the further point has been established that tendency to elimination along an alkyl branch $R{\cdot}CH_2{\cdot}C_\alpha$ varies with R according to the order $H<\{Me>Et, Pr^n, \text{etc.}\}$. Also for reaction (*b*), it has been found that the composition of the amylenes which are produced from *tert.*-amyl alcohol is similar to that of the amylenes formed from *tert.*-amyl bromide, or from a dimethyl-*tert.*-amylsulphonium salt, when, in these cases, decomposition proceeds by the unimolecular mechanism. For both reactions (*a*) and (*b*), it has been established that tertiary alcohols can be dehydrated with ease, secondary alcohols with considerably greater difficulty, and primary alcohols scarcely at all. The catalysts suggest oxonium ion intermediates, and a comparison of all the above results with our data for sulphonium ions points decidedly to the conclusion that these intermediates are undergoing elimination by the unimolecular mechanism (*E*1). Thus we suggest the following detailed mechanisms:

$$(a)\quad \left\{\begin{array}{l} R{\cdot}OH + \overset{+}{O}H_3 \underset{\text{fast}}{\rightleftharpoons} R{\cdot}\overset{+}{O}H_2 + OH_2 \\ R{\cdot}\overset{+}{O}H_2 \xrightarrow[\text{slow}]{} \overset{+}{R} + OH_2 \\ \overset{+}{R} \xrightarrow[\text{fast}]{} \text{Olefin} + \overset{+}{H} \end{array}\right\} \quad (E1)$$

$$(b)\quad \left\{\begin{array}{l} R{\cdot}OH + 2I_2 \underset{\text{fast}}{\rightleftharpoons} R{\cdot}\overset{+}{O}HI + \bar{I}_2 \\ R{\cdot}\overset{+}{O}HI \xrightarrow[\text{slow}]{} \overset{+}{R} + HOI \\ \overset{+}{R} \xrightarrow[\text{fast}]{} \text{Olefin} + \overset{+}{H} \end{array}\right\} \quad (E1)$$

Reactions (*a*) should be paralleled, with all the consequences we have already illustrated, by the acid-catalysed formation of olefins from ethers, as we have, indeed, partly confirmed by experiments which are not yet complete enough to publish. The postulated pre-equilibrium of reactions (*b*) seems consistent with Fairbrother's ideas (*Nature*, **1947**, **160**, 87), and can be supported by the special observation, details of which are reserved for inclusion in a later paper, that iodine is a moderately good electrolyte in *tert.*-butyl alcohol as solvent. We may note the implicit assumption in these explanations that bimolecular elimination (*E*2) from alkyloxonium ions would be controlled essentially by the inductive effect, with the result that orientation would follow Hofmann's rule and its various generalisations.

One further example may be given, *viz.*, the formation of olefins from sulphonic esters, either by the action of an alkali, such as sodium ethoxide, or in the course of solvolysis in a neutral or acid alcoholic solution. The conditions in which sulphonic esters enter into bi- and uni-molecular reactions have been made the subject of an investigation by Dr. C. A. Bunton, which will be published later. He has shown that the total reaction, substitution plus elimination, of *iso*propyl toluene-*p*-sulphonate with 0·3N-sodium methoxide in methyl alcohol is kinetically of the second order, and is, accordingly, bimolecular in mechanism. He has also shown that the total solvolysis of the same ester in 50% aqueous methyl alcohol is a reaction of the first order; and that since it is not detectably accelerated by added sodium hydroxide and methoxide up to an alkali concentration of 0·05N, it is certainly unimolecular in mechanism. We may conclude that the toluene-*p*-sulphonate of most secondary alcohols will readily enter into bimolecular reactions with alkoxide ions in alcohols, but will tend to undergo unimolecular decompositions on alcoholysis or hydrolysis in the absence of alkali. Now W. Hückel, Tappe, and Legutke (Refs. 35 and 48 of Sections 1.1 and 1.2), without actually applying any form of kinetic control to their reactions, analysed the mixtures of isomeric olefins which were formed from the toluene-*p*-sulphonates of a number of secondary alcohols, not only by the action of ethoxide ions, but also under conditions of solvolysis in the absence of alkali. The alcohols they employed were cyclic, and, for such compounds, a stereochemical condition requires to be fulfilled, as we shall

discuss in the next Section; but for the present we shall avoid going into this matter by restricting illustration to cases in which the condition is satisfied. Hückel, Tappe, and Legutke found that, in neutral solvolysis by ethyl alcohol, *cis*-1-decalyl I-toluene-*p*-sulphonate gave mainly 1 : 9-octalene, whilst *trans*-2-decalyl I- or II-toluene-*p*-sulphonate yielded chiefly 2 : 3-octalene; *i.e.*, the double bonds entered principally into the positions marked by asterisks in the following formulæ :

Formula (V) corresponds to Saytzeff's rule, and formula (VI) to a theoretically deduced extension of Saytzeff's rule given in the preceding Section (p. 2104). Thus, the general picture is one of control by the electromeric effect, as we should expect from our assumption that elimination in solvolysis follows the unimolecular mechanism (*E*1). What is more interesting, however, is that Hückel, Tappe, and Legutke found these esters to display qualitatively the same orientations in the eliminations which they undergo in the presence of considerable concentrations of alcoholic sodium ethoxide. From this we must conclude that the bimolecular eliminations (*E*2) of alkyl toluene-*p*-sulphonates, like those of alkyl halides, are controlled by the electromeric effect.

From a consideration of all the eliminations thus far discussed, it would appear that the circumstances in which either the inductive effect or the electromeric effect may exert a dominating influence over the velocity and orientation of elimination by different mechanisms from different kinds of alkyl compound may be defined as follows : (i) When the electron-attracting atom attached to the alkyl group carries a positive ionic charge, bimolecular elimination will be controlled by the inductive effect. (ii) When this atom does not carry a positive charge, bimolecular elimination will be controlled by the electromeric effect. (iii) Independently of the nature of the electron-attracting atom, unimolecular elimination will be governed by the electromeric effect. The discussed examples may be classified as indicated in the following scheme :

(i) Inductive control of *E*2 . . . Y = $\overset{+}{N}R_3$, $\overset{+}{P}R_3$, $\overset{+}{S}R_2$, $\overset{+-}{S}O_2R$

(ii) Electromeric control of *E*2 . . Y = Cl, Br, I, O·SO_2R

(iii) Electromeric control of *E*1 . . Y = $\overset{+}{S}R_2$, $\overset{+}{O}R_2$, Cl, Br, I, O·SO_2R

The type of alkyl group, whether primary, secondary, or tertiary, has no concern with the matter. It should be emphasized that the above statements apply to heterolytic 1 : 2-eliminations in solution : we do not consider elimination by reactions, such as the oxidation of hydrazones and the pyrolysis of xanthates, which are probably homolytic; and, of course, we are excluding gas and surface reactions from our discussion.

The type of alkyl group has, of course, a vital concern with the replacement of bimolecular mechanisms by unimolecular mechanisms of substitution and elimination. Under given conditions as to reagent and solvent, and for a given electron-attracting group Y, the tendency to such replacement follows the order primary-to-tertiary of alkyl groups, as one may understand on the grounds that increasingly powerful polar effects of alkyl will favour the separate heterolysis of the bond C_αY. For given conditions as to reagent and solvent, and for a given alkyl group, the tendency to replacement of bimolecular elimination by unimolecular substitution and elimination varies with the electron-attracting group Y. Apparently the variation here follows the inverse order of the inductive effect, as one may partly rationalise on the basis that an increasing inductive effect must increase the vulnerability of the β-hydrogen atom towards basic reagents. Schematically, we have the following general relations :

Constitutional promotion of change *E*2→*E*1 } { Alk . . . . Primary < Secondary < Tertiary
Y . . . . . $\overset{+}{N}R_3$ < $\overset{+}{S}R_2$ < Hal < O·SO_2R

The environmental factors which favour the change *E*2→*E*1 have already been considered in Part V (*J.*, 1940, 899) : the most important are the basicity and concentration of the reagent, and the ionising power of the solvent.

It can scarcely be doubted that the existence of separate fields of control by the inductive and electromeric effects on the velocity and orientation of the elimination reactions of alkyl derivatives is to be taken to mean that, in principle, both effects are always present, but that, owing to circumstances still to be considered, either one or the other dominates. Several

apparent indications of a modifying influence of a minor effect on a broad result determined by a major one have been already noticed in this discussion. We may instance the accelerating effect of α-alkyl substituents in bimolecular elimination from sulphonium ions (pp. 2100 and 2101), and the considerably greater accelerations produced by a β-phenyl than by an α-phenyl substituent in bimolecular eliminations from alkyl halides (p. 2105). However, in order to obtain decisive effects, let us go outside the field of alkyl groups, and examine, on the one hand, more polar groups, and, on the other, more unsaturated groups; for then we shall find that inductive or electromeric effects, as the case may be, which would have been masked in the corresponding alkyl compounds, can be made quite clearly to dominate.

Consider, for example, the second-order eliminations of alkyl halides : they obey the Saytzeff rule, and are controlled essentially by the electromeric effect : the influence of the inductive effect is only of minor importance. However, if we introduce into the alkyl group a strongly electron-attracting β-halogen substituent, then the inductive effect of this polar substituent so loosens the β-proton that the elimination reaction is very greatly accelerated. We can show that this is not essentially an electromeric effect, due to a conjugation of the unshared electrons of the β-halogen atom with the developing double bond, though such an effect also would produce an acceleration. For the electromeric effect should work just as well from the α-position, and therefore, if we take the corresponding α-halogenoalkyl halide, instead of the unsubstituted alkyl halide, as the standard of comparison, we shall isolate the inductive effect, which is primarily a property of β-linked substituents. Such a comparison was made by Olivier and Weber (Ref. 25 of Section 1.1), when they measured the second-order rate-constants for the conversion of ethylene bromide, and of ethylidene bromide, into vinyl bromide by means of hydroxide ions in " 33% " aqueous acetone at 30°. The relative bimolecular rates were as follows :

$$(Br)CH_2{\cdot}CH_2Br \text{ (rate = 205)} \qquad CH_3{\cdot}CH(Br){\cdot}Br \text{ (rate = 1)}$$

The much larger rate associated with the presence of the β-bromo-substituent shows that, owing essentially to the polarity of the substituent, the inductive effect is in control—as it would not have been if the β-substituent had been an alkyl radical. Olivier himself assumed a controlling electrostatic effect, pointing out that it correctly interpreted numerous orientational results relating to the elimination reactions which polyhalogeno-paraffins undergo in the presence of alkalis. The following examples are instructive :

$$CHCl_2{\cdot}CH_2Cl \xrightarrow[E2]{} CCl_2{:}CH_2$$

$$CH_3{\cdot}CBr_2{\cdot}CHBr{\cdot}CH_3 \xrightarrow[E2]{} CH_3{\cdot}CBr{:}CBr{\cdot}CH_3$$

In the first case the lost halogen atom is the single one, whilst in the second case it is one of the pair. This shows that the attachment of a second halogen atom to the carbon atom from which a halogen atom is lost (the carbon atom we label α) is not a governing orientational factor. It is the attachment of halogen to the carbon atom from which hydrogen is lost (the carbon atom we label β) which is the governing circumstance—as we should expect, if it is the inductive effect, rather than the electromeric effect, which is in control. The rule is always that, of the various hydrogen atoms which could be eliminated in association with any of the halogen atoms, the one actually eliminated, along with an appropriate halogen atom, is that which is attached to the most halogenated, and therefore most positive, carbon atom. This points decidedly to a controlling inductive effect.

Similar evidence convinced Olivier that the carboxyl substituent directs the course of eliminations by means of its inductive effect. This substituent also has the property of unsaturation, as well as a strong polarity; and thus, in principle, it is capable of exerting an electromeric, as well as an inductive, effect. However, it actually operates mainly by virtue of its inductive effect, as we could show, for example, by reference to the much greater rates of formation of olefinic acids from β-halogeno- than from α-halogeno-acids or their derivatives.

We obtain evidence of a complementary kind when we turn to the bimolecular eliminations of 'onium salts (where, for ordinary alkyl groups, the inductive effect controls orientation), and for this series of reactions consider the behaviour of substituents of low polarity and high unsaturation. Phenyl and vinyl are amongst the chief examples, and it was with the aid of the former that the first case of breakdown of the Hofmann rule was realised (Ref. 1 of Section 1.1). Notwithstanding, the distinct polarity of phenyl in attachment to a saturated side-chain, the phenyl substituent in 2-phenylethyl-ammonium, -phosphonium, and -sulphonium ions, and in 2-phenylethyl sulphones, accelerates elimination to so great an extent that we must ascribe a considerable part of the effect to the capacity of the substituent for conjugation. The total

effect may be illustrated, in its application to sulphonium ethoxides, by reference to the following relative rates of bimolecular eliminations from ethyl- and 2-phenylethyl-sulphonium ions in ethyl alcohol at 64° (Part XII):

$CH_3{\cdot}CH_2{\cdot}\overset{+}{S}Me_2$ (rate = 1) $\quad$ $Ph{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2$ (rate = 430) $\quad$ $CH_3{\cdot}CHPh{\cdot}\overset{+}{S}Me_2$ (rate = 96)

The relative rate for the corresponding 1-phenylethylsulphonium ion under the same conditions (Part XIII) is noted for comparison. For the acceleration produced by the α-phenyl substituent must represent an essentially pure electromeric effect, and its considerable magnitude confirms our assignment of a large part of the acceleration produced by the β-phenyl substituent to the unsaturation, rather than to the polarity, of this radical.

The above facts show that the inductive and electromeric effects jointly influence elimination, their relative importance depending on the polarity and unsaturation of the influencing group. But, when both the polarity and the unsaturation are small, as with alkyl groups, the relative importance of the two effects can be seen to depend also, indeed primarily now, on the system which is being influenced. Let us consider this factor.

We know that when, in the bimolecular mechanism (*E*2), the influenced system is of the form $HC_\beta{\cdot}C_\alpha{\cdot}\overset{+}{Y}$ (where $\overset{+}{Y} = \overset{+}{N}$, $\overset{+}{P}$, or $\overset{+}{S}$), the inductive effect dominates; that when it is of the type $HC_\beta{\cdot}C_\alpha{\cdot}Y$ (where Y = Cl, Br, I, or OAc), the electromeric effect takes charge; and that when, in the unimolecular mechanism (*E*1), it is $HC_\beta{\cdot}\overset{+}{C}_\alpha$(sextet), once more the electromeric effect is in control. We know also from the quantitative results that the predominance of the electromeric effect is greater in this last case: we find larger effects on reaction rate, and more extreme orientation of the Saytzeff type, in unimolecular elimination with either 'onium salts or halides, than in bimolecular elimination with halides. Empirically then, the electromeric effect increases in relative importance as the influenced system takes the successive forms

(i) $HC_\beta{\cdot}C_\alpha{\cdot}\overset{+}{Y}$, $\quad$ (ii) $HC_\beta{\cdot}C_\alpha{\cdot}Y$, $\quad$ (iii) $HC_\beta{\cdot}\overset{+}{C}_\alpha$ (sextet);

and there is a large, qualitatively important, difference of behaviour between systems (i) and (ii), and a relatively much smaller, but quantitatively appreciable, difference between systems (ii) and (iii).

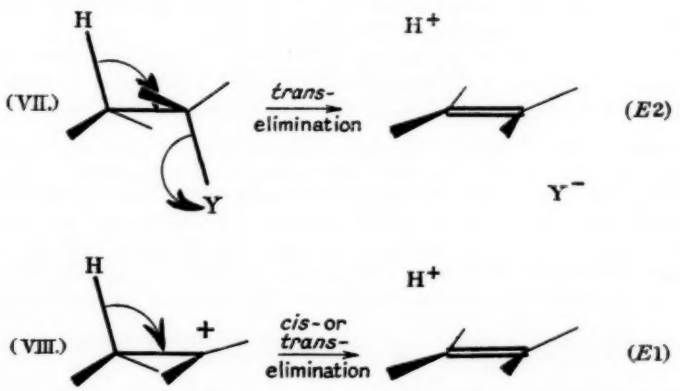
From a theoretical point of view, one may say that the differences must arise from different states of balance between the magnitude of the positive charge induced on C_β (which controls the intensity of the inductive effect of attached alkyl substitutents, Alk → C_β), and the degree of unsaturation developed in the transition state (which governs the strength of the electromeric effect due to hyperconjugation, *e.g.*, $H{-}\overset{\curvearrowright}{C}{-}C_\beta{=}\overset{\curvearrowright}{C}_\alpha$). We can immediately see that the inductive effect will be greater in system (i) than in system (ii), because of the stronger electrostatic effect of a positive pole than of any electrically uncharged atom. Further, we may expect the electromeric effect to be greater in system (ii) than in system (i), because solvation assists the heterolysis of the C—Y bond, but not of the $C{-}\overset{+}{Y}$ bond; wherefore the transition state of system (ii) tends to involve a relatively large electron-transfer (and hence a large development of unsaturation) in order to form the charges needed to produce the solvation energy. As to system (iii), it is clear that the electromeric effect will be much greater in this than in either of systems (i) or (ii), because of the intense unsaturation created by the pre-formed sextet; however, it is also clear that the inductive effect will be much greater in system (iii) than in the other systems, because of the proximity of the carbonium ionic centre to C_β. Collecting these points together, we see that theory can unequivocally account for the large difference of behaviour, to which co-operating factors contribute, between the systems (i) and (ii), but is ambiguous, because of the co-existence of counteracting factors, with respect to the much smaller difference between systems (ii) and (iii).

Sectional Summary.—In this Section we define the limits of structure and mechanism within which different kinds of constitutional factors exert a governing influence on the elimination reactions of alkyl compounds. Over the range cases studied, control by the inductive effect, leading to orientation according to Hofmann's rule and its generalisations, arises in bimolecular eliminations when the electron-attracting group carries a positive charge; and control by the electromeric effect, leading to orientation as given by Saytzeff's rule and its generalisations, occurs in bimolecular eliminations when the electron-attracting group is uncharged, and in all unimolecular eliminations. We have illustrated the effects on rate and orientation of crossing the boundary between these separate domains of control; and we have shown that some less fully investigated eliminations can be fitted into the general scheme.

By extending our survey beyond the range of alkyl compounds, we perceive that a substituent of sufficient polarity will exert a dominating inductive effect on an elimination in any system; and that a sufficiently unsaturated substituent will exert a dominating electromeric effect in any system. Only when both the intrinsic polarity, and the intrinsic unsaturation, of the substituent are small, as with alkyl substituents, will the system itself play a controlling role. And this it will do by calling out the latent polarity or unsaturation in the substituent by means of its own polarity or unsaturation, either as these characters exist permanently, or as they are developed in the transition state of reaction. The inductive effect, which arises from the electrostatic polarity of substituents, is exerted from the commencement of reaction. The electromeric effect, which derives from a quantal resonance of electrons having properties of unsaturation, is developed only during reaction, and thus becomes of main importance in the transition state. On these lines we can form a consistent picture of general constitutional influences on eliminations, and of the special complications that apply to alkyl compounds.

(3.5) *Stereochemical Factors in Elimination.*—As Hückel, Tappe, and Legutke have already appreciated (Ref. 35, Section 1.1), the rules which govern the stereochemical course of substitution at an aliphatic carbon atom (Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252) are likely to have a close parallel in relation to elimination. In collaboration with Dr. R. Pasternak and Dr. Dorothy Usher, the task of establishing this by kinetic methods has recently been undertaken; and, though the work is not yet complete enough for report, we shall here anticipate its record for the purpose of discussing the stereochemical aspects of the orientation of elimination. For many of the statements which we have made above concerning the orientation of elimination apply only to systems which either are already in, or are easily capable of assuming, appropriate configurations; and these statements, therefore, require some qualification, especially in their application to certain olefinic and cyclic compounds, which it is necessary now to define.

The principal stereochemical restriction is that, in bimolecular eliminations (*E*2) of the system H—C_β—C_α—Y, where Y may be either neutral or charged, the β-CH electrons must if possible enter the octet of C_α on the side remote from Y; for this is the way in which the exchange integrals of electrons of different pairs, and therefore the total energy, of the transition state can be kept as small as is possible (cf. Cowdrey, Hughes, Ingold, Masterman, and Scott, *loc. cit.*): the result is exclusive *trans*-elimination (VII). Cristol has recently shown (*J. Amer. Chem. Soc.*, 1947, **69**, 338) that, whilst *trans*-elimination from hexachloro*cyclo*hexanes, where permitted by the structure, takes place with ease in bimolecular reactions with alkali, *cis*-elimination can scarcely be realised under the same conditions when *trans*-elimination is excluded by the structure. In unimolecular elimination (*E*1), on the other hand, the C_β-carbonium ion tends to the same planar form, from whichever side of the plane the electron-attracting group Y has separated. Therefore, both *cis*- and *trans*-elimination are normally possible (VIII) by the unimolecular mechanism, though if the carbonium ion is very short-lived, *trans*-elimination may be favoured, and in the presence of special substituents *cis*-elimination may predominate (cf. Cowdrey *et al.*, *loc. cit.*).

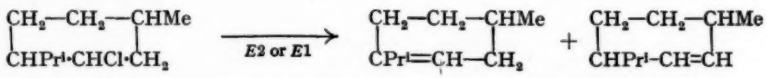


Another steric effect, which would likewise apply to bimolecular eliminations only, might arise from screening of the β-hydrogen atoms from attack by the nucleophilic reagent. This ordinary sort of steric hindrance seems to be definitely less important for eliminations than for

bimolecular substitutions, probably because of the relatively more exposed situation of the hydrogen atoms than of the carbon atoms in all the simpler alkyl groups. This effect, moreover, though it is appreciable in special structures, is considerably less important than that of the stereochemical course of elimination, and therefore we shall not attempt to isolate the former in the approximation to which, at present, we are discussing steric effects.

Even when the system $>CH\cdot CRY\cdot CH_2-$ forms part of a ring, an elimination of HY towards the methylene group is always stereochemically possible, because one or other of the methylene hydrogen atoms either is in, or can be brought into, an appropriate configuration, when the mechanism makes this necessary. But, in rings of seven atoms or less, an elimination towards the methine group may be precluded, however much polar factors might favour such a process; and it will be so precluded if the mechanism is bimolecular (*E*2), and if, in addition, the methine hydrogen atom is firmly oriented in a *cis*-position with respect to the electron-attracting group Y. (We restrict this statement to rings of seven atoms or less, because, in rings of eight atoms or more, *cis*-related bonds of neighbouring carbon atoms can be brought into an approximately antiparallel orientation by strainless rotations about the ring bonds.)

On account of polar factors, in particular the electromeric effect, alkyl halides, if free from stereochemical restrictions, undergo eliminations oriented according to Saytzeff's rule, both when the mechanism is bimolecular and when it is unimolecular. Thus the unrestricted system $>CH\cdot CRHal\cdot CH_2-$ should eliminate HHal by either mechanism in predominating amount towards the methine group. The inclusion of the system in, say, a six-membered ring should offer no interference to the operation of this rule, unless the mechanism is bimolecular (*E*2), and unless, in addition, the atoms which chiefly should be eliminated according to the rule are in *cis*-relation to each other. But, where both these circumstances arise, the Saytzeff rule will become abrogated, as may be illustrated by the following examples, which are due to Hückel, Tappe, and Legutke (*loc. cit.*) :



(+)-*neo*Menthyl chloride + $\bar{O}Et \xrightarrow{E2}$ 3-Menthene (~75%) + 2-Menthene (~25%)

(−)-Menthyl chloride + $\bar{O}Et \xrightarrow{E2}$,, (0%) + ,, (100%)

(−)-Menthyl chloride (Solvolysis) $\xrightarrow{E1}$,, (~70%) + ,, (~30%)

In *neo*menthyl chloride the groups Pr^i and Cl are on the same side of the *cyclo*hexane ring, whereas in menthyl chloride they are on opposite sides. Hence *neo*menthyl chloride is not sterically precluded from undergoing bimolecular elimination in that direction which should predominate according to the Saytzeff rule, and which does, in fact, predominate in this case. But, because of its configuration, menthyl chloride cannot undergo bimolecular elimination in that direction, not even in minor amount. No such restriction applied to unimolecular elimination, and accordingly, menthyl chloride can, and does in fact, undergo this form of elimination to a predominating extent in agreement with Saytzeff's rule.

On account of polar factors, in particular the inductive effect, alkylammonium ions, if free from stereochemical restrictions, undergo eliminations which are oriented according to Hofmann's rule and its generalisations, provided that the mechanism is bimolecular (*E*2). Thus the unrestricted system $>CH\cdot CR(\overset{+}{N}Me_3)\cdot CH_2-$ should undergo bimolecular elimination oriented in predominating amount towards the methylene group. If the system is included in, say, a six-membered ring, one of the two methylene hydrogen atoms will invariably be situated in such a position as to allow elimination in this direction. Even so, one can recognise the modifying effect on orientation of a *cis*-relation between the methine hydrogen atom and the ammonium group; for such a relation converts what would have been merely a predominating orientation into an exclusive one, as may be seen by the following examples (*idem, ibid.*) :

(+)-*neo*Menthyl-$\overset{+}{N}Me_3$ + $\bar{O}H \xrightarrow{E2}$ 3-Menthene (~20%) + 2-Menthene (~80%)

(−)-Menthyl-$\overset{+}{N}Me_3$ + $\bar{O}H \xrightarrow{E2}$,, (0%) + ,, (100%)

This result shows that *trans*-elimination in the bimolecular reactions of alkyl halides is not due to the direction of an anionic reagent by the electrostatic field of the C–Hal dipole, any

more than the Walden inversion in bimolecular substitution is due to this cause. For in the $C\text{–}\overset{+}{N}$ link, the dipole and the related electrostatic field are reversed, and yet, in bimolecular reactions with anionic reagents, we still find *trans*-elimination, just as in substitutions we still observe the Walden inversion (cf. Cowdrey, Hughes, Ingold, Masterman, and Scott, *loc. cit.*). The cause in all cases is the same, *viz.*, the need to economise energy in the transition state by the minimisation of bond-overlap : the quantal forces here involved are of much greater importance than dipole forces.

Some of the above points could also have been illustrated by the production of isomeric octalenes from stereoisomeric 1-decalyl compounds (Hückel, Tappe, and Legutke, *loc. cit.*). Certain examples, likewise belonging to the *cyclo*hexane series (but lacking evidence of mechanism), have been recorded, in which polar effects due to phenyl and carbethoxyl substituents on the direction of elimination have become inverted by stereochemical causes (Price and Karabinos, *J. Amer. Chem. Soc.*, 1940, **62**, 1159; Price and Schwarcz, *ibid.*, p. 2891). As an illustration representing the ethylene series, reference may be made to work of Chevanne (*Bull. Soc. chim. Belg.*, 1912, **26**, 287), showing that *cis*-1 : 2-dichloroethylene is converted into chloroacetylene by treatment with ethyl-alcoholic potassium hydroxide (the probable mechanism therefore being *E*2) much more easily than is the *trans*-isomeride.

Sectional Summary.—The previously discussed polar effects on the velocity and orientation of eliminations apply without qualification only to systems which either are already in, or can easily be brought into, an appropriate stereochemical configuration. The chief stereochemical restriction is that the β-CH electrons of $HC_\beta{\cdot}C_\alpha{\cdot}Y$ must if possible enter the octet of C_α on the side remote from Y : this applies only to bimolecular elimination; but it then applies no matter whether Y is a formally neutral group, or whether it carries a positive ionic charge. The requirement arises from the need to minimise bond-overlap in the transition state. Examples of cyclic systems are given in which the orientation of elimination is changed by this factor from what it would have been under control by the inductive and electromeric effects only.

In Part V (*J.*, 1940, 899) environmental influences on the bimolecular and unimolecular mechanisms of elimination were considered : certain sections of this subject have been more extensively treated in Parts VII and VIII (this vol., pp. 2043, 2049). These three papers, together with the present paper on constitutional influences, are intended collectively to constitute a balanced statement of the present position of the theory of heterolytic 1 : 2-eliminations. Investigations on other forms of elimination have been instituted, but have not yet reached a condition suitable for report.

We have to thank Messrs. Imperial Chemical Industries Ltd. for help with the cost of these researches; and also the Department of Scientific and Industrial Research for personal grants made to several of us.

Sir William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1. [*Received, January 15th*, 1948.]

---

427. *The Kinetics of Photochemical Oxidation with Dichromate : The Oxidation of Glycerol.**

By K. Weber and S. Ašperger.

The kinetics of the photochemical oxidation of glycerol by dichromate under the influence of polychromatic light have been investigated. Particular stress has been laid upon the influence of temperature, addition of acid or of alkali, and also upon the rôle of the simultaneous thermal reaction. Under certain conditions of experiment (high concentration of glycerol), the existence of a *negative temperature coefficient* was established.

A reaction mechanism has been developed, by means of which, on the supposition of a preceding equilibrium, the negative temperature effect can be explained. The hydrolysed dichromate ion must be considered as the photochemically active component. A new calculation of the heat of hydrolysis gave the value −1186 cals./mol., in good agreement with the caloric effect of the temperature-function of the reaction velocity, *viz.* −1210 cals./mol. The reaction mechanism makes it possible to account also for the other results of the kinetic measurements.

In spite of many investigations (Goldberg, *Z. wiss. Phot.*, 1906, **4**, 95; Luther and Forbes, *J. Amer. Chem. Soc.*, 1909, **31**, 770; Forbes *et al.*, *ibid.*, 1923, **45**, 1891; 1932, **54**, 960; 1933, **55**, 588,

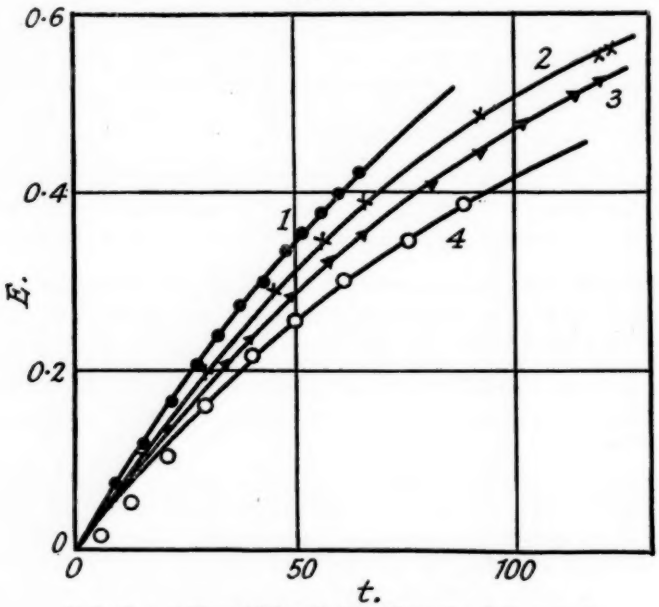
* A short preliminary communication on this subject appeared in *Nature*, 1946, **157**, 373.

2407; Dhar, *J.*, 1923, **123**, 1856; Bowen *et al.*, *J.*, 1927, 2353; 1929, 1648; 1931, 1866; 1932, 2081; Bhattacharya and Dhar, *Z. anorg. Chem.*, 1928, **169**, 381; Morton, *J. Physical Chem.*, 1929, **33**, 1135; Riesenfeld and Hecht, *Z. wiss. Phot.*, 1929, **26**, 369; Winther, *Z. physikal. Chem.*, 1935, *A*, **174**, 41) the oxidations by means of chromates and dichromates have not yet been elucidated in detail. We have now investigated the kinetics of the *photochemical* oxidation of glycerol, laying particular stress on the influence of temperature on the reaction velocity, as it has been found that this reaction, if specific conditions are fulfilled, shows the rather rare phenomenon of a negative temperature coefficient. This has a particular bearing on the elucidation of the reaction mechanism.

Experimental.

The velocity of the photochemical reaction was determined by measuring photoelectrically the extinction of the oxidation product (*i.e.*, the green colour of the tervalent chromium). By exposing the reactants to white light and using appropriate light filters, the measurements could be conducted during the course of the reaction. The light used for the photochemical reaction served also for the photoelectrical measurement of the extinction.

Fig. 1.



$K_2Cr_2O_7$: 5·77 × 10^{-3} *mols./l.* *Glycerol:* 7·51 *mols./l.*

Dependence of reaction velocity on temperature: E = *extinction*, t = *time of reaction in minutes. Curve* 1 *gives the values for* 14°, 2 *for* 25°, 3 *for* 35°, *and* 4 *for* 45°.

The reaction vessel, made of plane parallel glass plates (5 × 5 × 1 cm.), was placed in a thermostat (constant within ±0·1°), and the contents stirred mechanically during exposure to a 500-watt incandescent or to a mercury-vapour high-pressure lamp. Close behind the reaction vessel, screened by a yellow filter, there was a selenium photoelement whose current was measured with a reflection galvanometer.

The numerical value of the coefficient of extinction, necessary for the calculation of the velocity of the photochemical reaction, was computed directly from kinetic measurements. As the experiments were conducted with polychromatic light, the *actinometric* determinations gave the " mean " coefficient for the spectral interval that was—in the given experimental arrangement—chemically active. It did not seem necessary to use monochromatic light, as it could be assumed that in the whole spectral interval used for the exposure, the absorption yields the same chemical result. This supposition was eventually confirmed by the results of the experiments.

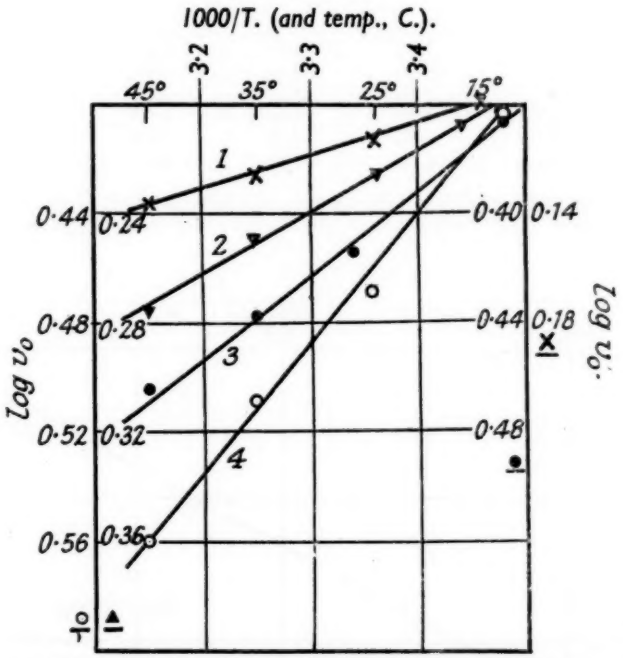
The reaction velocities were measured with different concentrations of the two components and at temperatures of 14—45°. The influence of the intensity of light on the reaction was also determined.

Fig. 1 shows some of the curves obtained for the velocity. From them a negative temperature coefficient can be inferred. The values of the ordinates of the tangents for the time of 50 minutes have been used as relative values of the initial velocities (v_0).

The results of experiments with a constant concentration of glycerol (7·51 mols./l.) and four different concentrations of dichromate at various temperatures are shown graphically in Fig. 2. The inclination

of all straight lines towards the abscissa indicates a negative temperature coefficient (Forster and Blich, *Z. angew. Chem.*, 1910, **23**, 2017; Skrabal, *Monatsh.*, 1912, **33**, 118; *Z. Elektrochem.*, 1915, **21**, 461; Skrabal and Weberitsch, *Ber.*, 1914, **47**, 117; Trautz, *Z. Elektrochem.*, 1915, **21**, 329; Bodenstein, *ibid.*, 1918, **24**, 183; *Z. physikal. Chem.*, 1922, **100**, 68; 1936, **175**, 294; *Helv. Chim. Acta*, 1935, **18**, 743; Padoa, *Gazzetta*, 1921, **51**, I, 3; Schumacher, *Z. physikal. Chem.*, 1927, **129**, 241; *Z. Elektrochem.*, 1929, **35**, 715; Kassel, *J. Physical Chem.*, 1930, **34**, 1777). This coefficient ($Q_{10} = k_{T+10}/k_T$) for the interval between 35° and 45° is 0·91—0·97. It increases as the dichromate concentration increases from $5{\cdot}77 \times 10^{-3}$ to $4{\cdot}62 \times 10^{-2}$ mols./l. With small concentrations of dichromate, the negative temperature coefficient disappears. For a concentration of glycerol of 1·11 mols./l. and a concentration of dichromate of $2{\cdot}31 \times 10^{-2}$ mols./l. we found a temperature quotient $Q_{10} = 1{\cdot}32$. With an increase of temperature the negative temperature coefficient decreases and Q_{10} approaches unity.

FIG. 2.



Cr_2O_7'' = (1) $4{\cdot}62 \times 10^{-2}$, (2) $2{\cdot}31 \times 10^{-2}$, (3) $8{\cdot}09 \times 10^{-3}$, (4) $5{\cdot}77 \times 10^{-3}$, *mols./l.*
Glycerol concentration = 7·51 *mols./l. in all cases.*

From the measured initial velocities v_0, the relative velocity constants k that are independent of changes in concentration can be calculated from the equation

$$v_0 = kI_0(1 - e^{-ip}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

if the absorption constant i is known and if a linear relation between the velocity of reaction and the intensity of light can be supposed. The validity of Beer's law for polychromatic light cannot be assumed without proof; in our case, however, it can be deduced from the experimental material by means of the equation

$$\frac{v_1}{v_2} = \frac{1 - e^{-ic_1}}{1 - e^{-ic_2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where the initial velocities v_1 and v_2 correspond to the concentration of the dichromate c_1 and c_2, while $p = 1$. With the help of this equation we have calculated i by two methods: first, by the development of the series of exponential expressions which give equations that can be solved for i (approximate method); secondly, by transforming equation (2) into

$$v_2 - v_1 = v_2(e^{-c_2})^i - v_1(e^{-c_2})^i \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

by means of a graphical method which, after numerical calculation of the expressions within the parentheses, gives i as a function of $v_2 - v_1$. For a number of arbitrarily chosen values for i, curves were obtained that enabled us to read the values for i that correspond to the actual values of $v_2 - v_1$.

Although the values for the absorption coefficient for the different concentrations of potassium dichromate differ appreciably, their mean values are almost identical. This is easy to understand, for it was established by special approximate calculation that the discrepancies in the i values are due, not so much to experimental error, as to inaccuracy of the methods of calculation. The values for the absorption coefficient are almost independent of temperature. The following values were found:

at 25°, $i = 99{\cdot}2$; at 45°, $i = 97{\cdot}2$. The mean value, *i.e.*, $i = 98{\cdot}2$, was used for the calculation of the relative velocity constant according to equation (1).

The linear dependence of the investigated velocity of reaction on the intensity of light is known from the literature, but it follows also from the results of our experiments, since equation (1) is established as valid. It is confirmed also by experiments conducted with the high intensities of the light of the mercury high-pressure lamp.

The velocity constants (k) calculated from the initial velocities by means of equation (1) are given in Table I ($I_0 = 100$). It is clear that the k values obtained for the same temperature agree well with each other independently of the concentration of potassium dichromate.

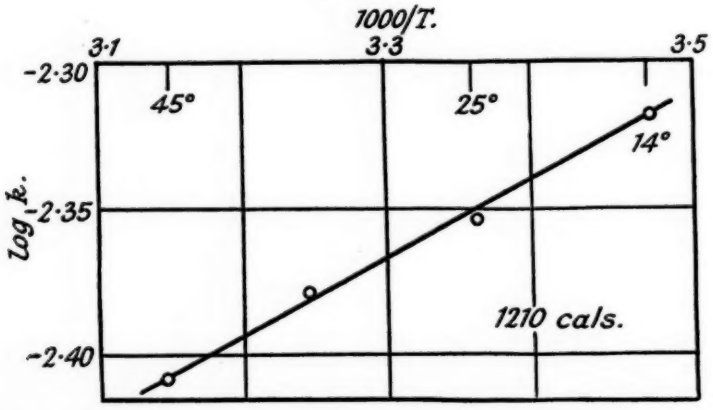
TABLE I.

Concentration of glycerol: 7·51 mols./l.

$K_2Cr_2O_7$, mols./l. × 10^3.	$k \times 10^3$.			
	14°.	25°.	35°.	45°.
5·77	5·09	4·74	4·23	3·84
8·09	4·93	4·31	4·19	4·09
23·1	4·29	3·90	3·79	3·48
46·2	4·92	4·76	4·53	4·25
Mean values	4·80	4·42	4·18	3·91

Fig. 3 shows the graphical evaluation of the temperature function of the velocity constant k according to the Arrhenius equation. The inclination of the straight line corresponds to an energy content of 1210 cals.

FIG. 3.



As the velocity of the concurrent thermal reaction is small, no account was taken of it during the photochemical measurements. The velocities of the reaction in the dark and in the light show a ratio of about 1 : 28 (see Fig. 4).

Addition of an acid (*e.g.*, hydrochloric) increases the velocity of the photochemical reaction but slightly. The increase is linear with the concentration of the acid. The thermal reaction, however, is accelerated considerably by the addition of acid: addition of $4{\cdot}62 \times 10^{-3}$M-hydrochloric acid increases the amount of the reaction products about 16-fold. In a decidedly acid medium the mechanism of the reaction takes a very complicated course.

Addition of alkali (sodium hydroxide) diminishes the velocity both of the thermal and of the photochemical reaction considerably. Solution of potassium chromate are therefore decidedly less photoactive than are analogous solutions of potassium dichromate (see Fig. 5). By means of experiments, the results of which are shown in Table II, we have investigated the quantitative influence of the concentration of hydroxyl ions on the velocity of the reaction. In the table, v denotes the experimentally obtained values for the velocity of the reaction at the start, and $I_{abs.}$ the % of light absorbed with regard to the concentration of the dichromate ions. Their concentration as well as that of $HCrO_4'$ ions has been calculated with the help of the hydrolytic and dissociation equilibrium constants for the Cr_2O_7'' ions and $HCrO_4'$ ions respectively. (The numerical values of those constants are discussed later.) From the reaction mechanism, as set forth in the present paper, the following equation for the influence of the concentration of hydroxyl ions can be deduced:

$$v = k' I_{abs.}/(k'' - [HCrO_4'][OH']) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

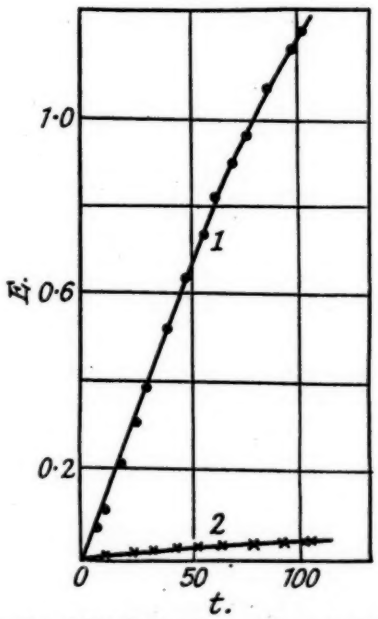
From our experimental data we have calculated the numerical values for k' and k''. The values obtained are also shown in Table II. As the values for k' and k'' are fairly constant, we infer that the above equation is valid, at least in principle. This statement further emphasises the intrinsic validity of the reaction mechanism discussed.

TABLE II.

$[K_2Cr_2O_7] = 2{\cdot}31 \times 10^{-2}$ mols./l.; [glycerol] = 7·51 mols./l.

[OH'].	$[HCrO_4']$.	$[Cr_2O_7'']$.	v.	$I_{abs.}$	$k' \times 10^{12}$.	$k'' \times 10^{10}$.
$4{\cdot}78 \times 10^{-10}$	$2{\cdot}14 \times 10^{-2}$	$1{\cdot}20 \times 10^{-2}$	0·606	69·23	5·39	6·25
					4·76	5·55
$7{\cdot}60 \times 10^{-9}$	$1{\cdot}94 \times 10^{-2}$	$7{\cdot}55 \times 10^{-3}$	0·590	52·36	4·54	5·62
					5·02	5·66
$4{\cdot}57 \times 10^{-8}$	$9{\cdot}28 \times 10^{-3}$	$1{\cdot}72 \times 10^{-3}$	0·570	15·54	4·58	5·49
					4·63	5·63
$1{\cdot}00 \times 10^{-7}$	$5{\cdot}08 \times 10^{-3}$	$5{\cdot}20 \times 10^{-4}$	0·523	6·23	4·70	5·65
					5·40	5·72
$2{\cdot}63 \times 10^{-7}$	$2{\cdot}10 \times 10^{-3}$	$1{\cdot}25 \times 10^{-4}$	0·432	1·22	5·21	5·67
					4·90	5·66

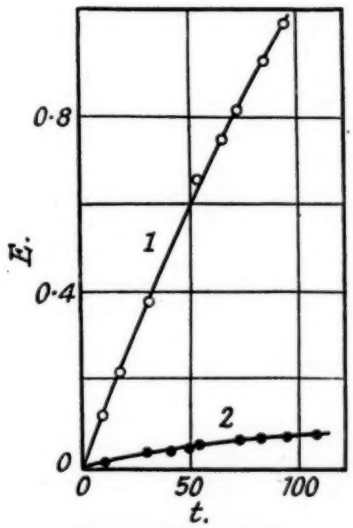
FIG. 4.



$K_2Cr_2O_7$: $2{\cdot}31 \times 10^{-2}$ *mols./l.* *Glycerol*: 7·51 *mols./l.*

(1) *Thermal and photochemical reactions.*
(2) *Thermal reaction only.*

FIG. 5.

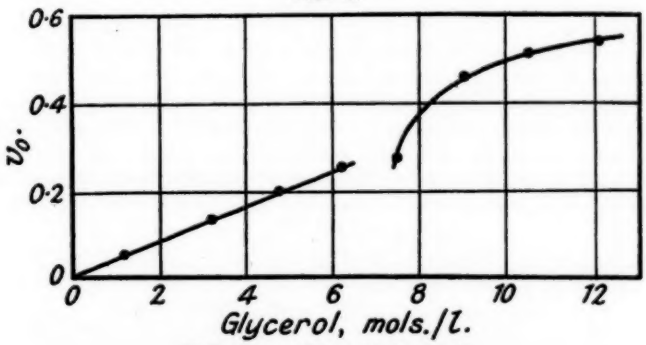


Glycerol: 7·51 *mols./l.*

(1) *Photo-reaction with* $K_2Cr_2O_7 = 2{\cdot}31 \times 10^{-2}$ *mols./l.*
(2) *Photo-reaction with* $K_2CrO_4 = 4{\cdot}62 \times 10^{-2}$ *mols./l.*

The influence of the concentration of glycerol on the velocity of the photochemical reaction has also been studied, and two concentration ranges of glycerol can be distinguished with regard to the velocity

FIG. 6.



$K_2Cr_2O_7$: $5{\cdot}77 \times 10^{-2}$ *mols./l.*

of the reaction. In the lower range (up to 6M) the increase of the initial velocity of the reaction is linear with increase of the concentration of glycerol. In the higher range (7—12M) this phenomenon is no

longer observed. Fig. 6 shows the results of measurements with $5{\cdot}77 \times 10^{-3}$M-dichromate, and analogous results have been obtained with concentrations of $2{\cdot}31 \times 10^{-2}$M. The non-linear curve in Fig. 6 can be expressed by the equation

$$v = 0{\cdot}6[C_3H_5(OH)_3]/\{0{\cdot}45 + [C_3H_5(OH)_3]\}$$

The values for the velocity of reaction at the start in Table III have been calculated by means of the above equation. The agreement between the found and the calculated values establishes the validity of the above equation, which has been inferred from the proposed reaction mechanism.

TABLE III.

$[C_3H_5(OH)_3]$, M.	v, found.	v, calc.
0·25	0·28	0·21
1·75	0·45	0·48
3·25	0·51	0·53
4·85	0·54	0·55

The Reaction Mechanism.—From the foregoing kinetic measurements and also from the fact that the photochemical oxidation of glycerol with dichromate shows a negative temperature coefficient it is possible to draw certain conclusions on the reaction mechanism. The few known cases of a negative temperature coefficient have been explained by assuming a chemical equilibrium that *precedes* the reaction determining the velocity. This equilibrium shifts with a rise of temperature in such a way that the concentration of one of the reagents *diminishes*, with resulting decrease of the reaction velocity. It can be easily seen that with such a reaction mechanism a negative temperature coefficient can be the more easily reached the *more* the preceding equilibrium is dependent on the temperature and the *less* this is the case with the reaction itself.

The velocity of *photochemical* reactions is, in general, almost independent of temperature, as the activation energy is furnished, at least for the greater part, by the absorption of the light. It must therefore be inferred that in photochemical reactions a negative temperature coefficient would be expected oftener than is actually the case if only reactions could be found where the preceding equilibrium showed the above-described dependence on temperature.

If we suppose that potassium dichromate, being a strong electrolyte, is completely dissociated in aqueous solution, we have for such solutions the following equations for its hydrolysis and dissociation :

$$(1)\ Cr_2O_7'' + H_2O \rightleftarrows 2HCrO_4' \quad \ldots\ldots\ldots\ (K_1)$$

$$(2)\ HCrO_4' \rightleftarrows CrO_4'' + H^{\cdot} \quad \ldots\ldots\ldots\ (K_2)$$

$$(3)\ HCr_2O_7' \rightleftarrows Cr_2O_7'' + H^{\cdot}$$

In neutral or weakly acid solution the equilibrium (3) is shifted strongly towards the right (compare the value of the dissociation constant given by Bowen and Jarnold, *J.*, 1929, 1648) so that in those solutions only equations (1) and (2) determine the concentration of the ions. The question arises : which of the equilibria precedes the photoreaction and which ion can therefore be considered as the photoactive component of the reaction ?

We suppose now that equation (1), *i.e.*, the hydrolysis of the dichromate ion, precedes the photoreaction and that the ion Cr_2O_7'' represents the photoactive component. In order to prove this supposition we shall compare the heat of reaction of this hydrolysis equilibrium with the value calculated according to the Arrhenius formula from the influence on the photo-oxidation of glycerol.

The heat of reaction of the equilibrium (1) has not been determined; it has, however, been calculated by LaMer and Read (*J. Amer. Chem. Soc.*, 1930, **52**, 3098) from their measurements of the heat of neutralisation of sodium dichromate by sodium hydroxide to be $-13{,}640$ cals./mol. In this calculation, the value of the equilibrium constant (1) to be used is important. The equilibrium constants in (1) and (2), *viz.*, $K_1 = [HCrO_4']^2/[Cr_2O_7'']$ and $K_2 = [H^{\cdot}][CrO_4'']/[HCrO_4']$ have been determined by various authors, but the values obtained differ considerably as can be seen from Table IV.

TABLE IV.

Temp.	K_1.	$K_2 \times 10^7$.	Authors.
25°	0·013—0·04	7·4—8·4	Sherrill [1]
18	—	6·0	Sherrill [1]
25	2·5	—	Beck and Stegmüller [2]
18	—	3·7	Beck and Stegmüller [2]
25	0·044—0·054	—	Stokes *et al.*[3]

[1] *J. Amer. Chem. Soc.*, 1907, **29**, 1641. [2] *Arb. Kais. Gesundh.*, 1910, **34**, 446.
[3] *Trans. Faraday Soc.*, 1941, **37**, 566.

LaMer and Read used the mean value of Sherrill's determinations, $K_1 = 0{\cdot}019$. This value is decidedly too low, as can be inferred from the fact that they obtained for the heat of dissociation of the hydrochromate ion, *i.e.*, for the equilibrium (2), a value of +780 cals./mol., which differs even in sign from the value calculated directly from the reaction isochore for the value of the dissociation constant (K_2) for various temperatures, *viz.*, −6772 cals./mol. On the other hand, the value for K_1 given by Beck and Stegmüller cannot be right either, because with it LaMer and Read's measurements cannot be interpreted at all. We have therefore used for our calculations a value of K_1 that is a mean of the data given by Stokes *et al.*, *viz.*, $K_1 = 0{\cdot}05$. With this value we were able to calculate from the measurements of LaMer and Read a value for the heat of hydrolysis of Cr_2O_7'' (−1186 cals./mol.) that agrees very well with the heat effect of our kinetic measurements (−1210 cals./mol.). Moreover, a value for the heat of dissociation of the hydrochromate ion was obtained (−7860 cals./mol.) that agrees fairly well with the dependence on temperature of the dissociation constant (−6772 cals./mol.).

We consider these facts as proof that in the photochemical oxidation with dichromate, the ion Cr_2O_7'' represents the photoactive component. Its hydrolytic equilibrium precedes the photochemical reaction. With the increase of temperature the equilibrium shifts in favour of the hydrochromate ion. This corresponds to a decrease of the concentration of the photoactive component and consequently to a diminished reaction velocity.

An excitation of the electron is possible in such a complex ion if the light energy is absorbed by an electron shift into the empty orbit of the ion. Whether such a light absorption would lead directly to a photochemical reaction is, however, questionable (Bonhoeffer and Harteck, "Grundlagen der Photochemie," Dresden, 1933, p. 165). We suppose, therefore, that the primary photochemical reaction consists in a shift of an electron within the hydrated dichromate ion. By taking up energy, the ion becomes so unstable that it disintegrates into OH', $HCrO_4'$, and CrO_3. For the photochemical oxidation of glycerol we must therefore suppose the following reaction mechanism :

$$Cr_2O_7'',HOH \rightleftarrows 2HCrO_4' - 1186 \text{ cals.}$$

(1) $Cr_2O_7'',HOH + Nh\nu \longrightarrow OH' + HCrO_4' + CrO_3$ . . . . . (k_1)

(2) $CrO_3 + HCrO_4' + OH' \longrightarrow Cr_2O_7'' + H_2O$ . . . . . (k_2)

(3) $CrO_3 + C_3H_5(OH)_3 \longrightarrow CrO_2 + C_2H_3(OH)_2{\cdot}CHO + H_2O$ . . . . (k_3)

(4) $CrO_3 + CrO_2 \longrightarrow Cr_2O_5$

(5) $Cr_2O_5 + C_3H_5(OH)_3 \longrightarrow C_2H_3(OH)_2{\cdot}CHO + Cr_2O_3 + H_2O$

This accounts in the first place for the fact that the photochemical oxidation with dichromate is followed by production of an alkaline reaction. The formation of glyceraldehyde has been established by Bowen and his collaborators (Bowen and Bunn, *J.*, 1927, 2353; Bowen and Yarnold, *J.*, 1929, 1648), and Eder (*J. pr. Chem.*, 1879, **14**, 294) found CrO_2 and Cr_2O_5 in chromate–gelatin that had been exposed to light.

In this reaction mechanism CrO_3, CrO_2, and Cr_2O_5 have to be considered as unstable intermediates. If one assumes their concentration during the stationary period to be constant, the photochemical reaction velocity, after the usual calculations are done, can be expressed as follows :

$$+\frac{d[Cr_2O_3]}{dt} = \frac{k_1 I_{abs.}[C_3H_5(OH)_3]}{k_2[HCrO_4'][OH']/k_3 + [C_3H_5(OH)_3]}$$

In this and in the following equations the value $I_{abs.}$ is given by

$$I_{abs.} = I_0(1 - e^{-kp[Cr_2O_7'',HOH]})$$

This expression has been confirmed in every respect by experiment. From it follows, first, the linear dependence of the reaction velocity on the intensity of light (I_0), and secondly, the exponential deceleration of the reaction and the increase of the concentration of the $HCrO_4$ ion on the addition of alkali. From the above expression a non-linear increase of the reaction velocity with the increase of the concentration of glycerol must be expected. If the concentration of glycerol is low, however, the following expression showing a linear connection is valid :

$$+\frac{d[Cr_2O_3]}{dt} \approx \frac{k_1 I_{abs.}[C_3H_5(OH)_3]}{k_2[HCrO_4'][OH']/k_3}$$

If the concentration of glycerol is high, the reaction velocity according to the expression $+d[Cr_2O_3]/dt \approx k_1 I_{abs.}$ becomes independent of this concentration.

All these deductions from the expression have been fully confirmed by experiment. It can be inferred therefrom that the reaction mechanism, as described above, corresponds in principle to the actual reaction.

THE UNIVERSITY, ZAGREB (CROATIA).

[*Received, October 6th*, 1947.]

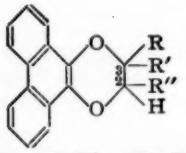
428. *Photochemical Reactions. Part XIII.* (a) *Photochemical Reactions of Ethylenes with Phenanthraquinone and with* 1 : 2 : 3-*Triketones.* (b) *Dimerisation Reactions in Sunlight.*

By Alexander Schönberg, Ahmed Mustafa, Mohamed Zaki Barakat, Nazih Latif, Radwan Moubasher, and Akila Mustafa (Mrs. Said).

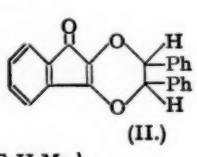
(*a*) Photochemical reactions of phenanthraquinone and *p*-methylstilbene, α-ethylstilbene, and 1-phenyl-2-β-naphthylethylene yield the substances (I*a*), (I*b*), and (I*c*), respectively. Similar reactions were carried out with triketoindane and stilbene and with *peri*naphthindane-7 : 8 : 9-trione (III) and stilbene, yielding the substances (II) and (IV), respectively.

(*b*) Photochemical polymerisation of α-naphthaquinone yields the colourless dimer (V); 1 : 2-benzanthracene yields the photo-dimer (VII). The bearing of this experiment on biological experiments with carcinogenic substances is stressed. The dimer (VIII) of 1 : 3-diphenylbenz*iso*furan, so far only obtained by a photo-process, was synthesised by a dark method.

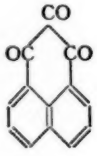
(*a*) The work on the action of stilbenes on phenanthraquinones (Schönberg and Mustafa, *Chem. Reviews*, 1947, **40**, 181; *J.*, 1944, 387; 1945, 551; 1947, 997) has been continued, and phenanthraquinone has been allowed to react in sunlight with *p*-methylstilbene, α-ethylstilbene, and 1-phenyl-2-β-naphthylethylene. The reaction products,* 3-*phenyl*-2-p-*tolyl*- (I*a*) 2 : 3-*diphenyl*-3-*ethyl*- (I*b*), and 3-*phenyl*-2-β-*naphthylphenanthro*(9′ : 10′ : 5 : 6)*dioxen* (I*c*), are colourless or almost colourless substances which, when heated, decompose into their generators. So far, photo-addition reactions of this type have been carried out with 1 : 2-diketones (*o*-quinones), but only now it has been found † that the reaction can be carried out also with



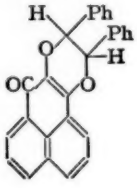
(I*a*; R = H, R′ = Ph, R″ = *p*-C_6H_4Me.)
(I*b*; R = Et, R′ = R″ = Ph.)
(I*c*; R = H, R′ = Ph, R″ = β-$C_{10}H_7$.)



(II.)



(III.)



(IV.)

1 : 2 : 3-triketones; thus triketoindane and *peri*naphthindane-7 : 8 : 9-trione (III) gave with stilbene the photo-addition products 1′-*keto*-2 : 3-*diphenylindeno*(2′ : 3′ : 5 : 6)*dioxen* (II) and 9′-*keto*-2 : 3-*diphenyl*per*inaphthindeno*(7′ : 8′ : 5 : 6)*dioxen* (IV). Their constitution is based on the fact that they are almost colourless, in contrast to the initial triketones which are dark red, and on the fact that the photo-addition products decompose on heating, with the re-formation of stilbene.

The scope of the photo-reaction between ethylenes and 1 : 2-diketones or 1 : 2 : 3-triketones may be seen from the following lists which give the names of the substances so far found active.

Ethylenes. Styrene, 1 : 1-diphenylethylene, stilbene, *p*-methylstilbene, *pp*′-dimethoxystilbene, α-ethylstilbene, 1 : 1-diphenylprop-1-ene, 1 : 1-di-(*p*-diphenylyl)-2-methylethylene, 1 : 1-dixenylethylene, 1 : 1-di-*p*-methoxyphenyl-2-methylethylene, α-stilbazole, β-chlorostilbene, 9-benzylidenexanthen, 9-benzylidenethioxanthen, benzylidenephthalide, methyleneanthrone, triphenylethylene, 1-phenyl-2-β-naphthylethylene, and diphenylketen.

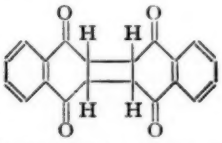
Ketones. Benzil, phenanthraquinone, retenequinone, triketoindane, and *peri*naphthindane-7 : 8 : 9-trione.

Phenanthraquinone reacts with all the ethylenes mentioned above, and stilbene with all those in the second list.

(*b*) (i) When the benzene solution of the yellow α-naphthaquinone is exposed to sunlight, the colourless photo-*dimer* (V) is formed.‡ The constitution of (V) is based on the following facts. The lack of colour makes a quinonoid structure improbable. The substance is not phenolic, for it is insoluble in alkali and does not react with diazomethane; it decomposes on heating at 270°, quantitatively or nearly so, with regeneration of α-naphthaquinone. As the dimer is difficultly

* These experiments were carried out by Nazih Latif.
† These experiments were carried out by R. Moubasher and Mrs. Said.
‡ These experiments were carried out by M. Z. Barakat.

soluble, no molecular-weight determination could be carried out. The assignment of a dimeric structure is based on the fact that 2-methyl-1 : 4-naphthaquinone gives, in sunlight, a

(V.) 

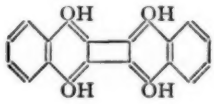
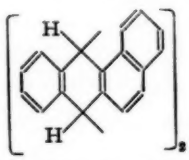
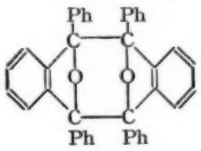
 (VI.)

photo-dimer (Madinaveitia, *Chem. Abs.*, 1935, **29**, 5438) which is soluble enough to allow of a molecular-weight determination. (V) is of interest because its hypothetical enolic form (VI) is related to diphenylene.

We were unable to prepare the photo-dimer of 2 : 3-dimethyl-1 : 4-naphthaquinone; the crystals were unchanged when exposed to sunlight, and no photo-reaction could be detected in their irradiated benzene solution.

(*b*) (ii) Very little is known about the photo-dimerisation of carcinogenic hydrocarbons. We found * that the weakly carcinogenic 1 : 2-benzanthracene (Shmuk and Guseva, *Chem. Abs.*, 1941, **35**, 3271) forms a difficultly soluble colourless photo-*dimer*, analogous to dianthracene, the photo-dimer of anthracene. The former dimer was obtained as a crystalline powder which is probably a mixture of isomers : whereas isomers are not possible for dianthracene, they are possible for di-1 : 2-benzanthracene (VII), which can be either an *s*- or an *as*-compound.

(VII.) 

 (VIII.)

The possibility of photo-dimerisation should not be overlooked when substances are tested for carcinogenic activity, where the material is applied externally. When 1 : 2-benzanthracene is tested, the animals should be kept in the dark to avoid photo-polymerisation of the material under investigation. A number of carcinogenic substances are now being investigated in this Department to discover whether they are changed † (formation of non-carcinogenic substances by the action of sunlight?). It is a remarkable fact that not only many carcinogenic hydrocarbons, but also a number of highly active carcinogenic compounds containing nitrogen, are derivatives of substances which undergo chemical reactions when their solutions are exposed to sunlight. Carcinogenic substances of this type are, *inter alia*, 4-dimethylaminoazobenzene (butter-yellow) and 2 : 3′-azotoluene, which are derivatives of azobenzene of which it is known that in solution the *cis*- and the *trans*-form are interconvertible in sunlight (Hartley, *J.*, 1938, 634). The carcinogenic derivatives of 4-aminostilbene (Haddow and Kon, *Brit. Med. Bull.*, 1947, **4**, 324) are derivatives of stilbene, which forms a dimer when its benzene solution is exposed to sunlight (Ciamician and Silber, *Ber.*, 1902, **35**, 4129).

(*b*) (iii) The photo-dimer (VIII) of 1 : 3-diphenyl*iso*benzfuran, obtained by the action of sunlight on the orange-yellow monomer (Guyot and Catel, *Bull. Soc. chim.*, 1906, **35**, 1127; Adams and Gold, *J. Amer. Chem. Soc.*, 1940, **62**, 2041), has not yet been obtained by a dark process. We found that when the monomer is heated at 270° in a sealed tube in dry carbon dioxide, and the melt is chilled in ice-water as quickly as possible, a good yield of (VIII) is obtained.

Parallel experiments were carried out with anthracene and α-naphthaquinone, but no dimerisation occurred.

Experimental.

The benzene was thiophen-free and dried over sodium. The photochemical reactions were carried out in Pyrex-glass tubes, the air having been displaced by dry carbon dioxide, and the tubes sealed.

Photo-reactions of Phenanthraquinone.—(i) *With* p-*methylstilbene.* Phenanthraquinone (1·09 g.) and *p*-methylstilbene (1 g.) (Meerwein *et al.*, *J. pr. Chem.*, 1939, **152**, 237) in benzene (50 c.c.) were exposed to sunlight for six days (October). Most of the benzene was then driven off; after some time,

* These experiments were carried out by A. Mustafa.

† It was found that 5- and 4′-methylbenzanthracene furnish in sunlight colourless photo-products of high melting point, which at room temperature are less soluble in benzene than the initial materials. These two substances were kindly supplied by Professor Haddow and Professor Kon (The Chester Beatty Research Institute of the Royal Cancer Hospital, London), but lack of material made further investigation impossible.

crystals appeared which were recrystallised from ethyl acetate. The addition *product* (I*a*) formed colourless crystals, m. p. 247° (decomp.; orange melt) (Found: C, 86·2; H, 5·4. $C_{29}H_{22}O_2$ requires C, 86·5; H, 5·5%); it gave a violet colour reaction with concentrated sulphuric acid at room temperature after a few minutes, and was soluble in benzene, but difficulty soluble in light petroleum (b. p. 50—70°); on pyrolysis, phenanthraquinone and *p*-methylstilbene were obtained.

The foregoing product was heated at about 270° (bath temp.) in a stream of carbon dioxide (the height of the decomposition tube being 25 cm.) for 15 minutes. The product was allowed to cool in a stream of carbon dioxide, and after 24 hours the crystals formed on the upper parts of the reaction vessel were extracted with hot light petroleum (b. p. 50—70°); the residue proved to be phenanthraquinone. The petroleum extract was concentrated and the resulting crystals, recrystallised from methyl alcohol, proved to be *p*-methylstilbene (m. p. and mixed m. p.).

(ii) *With α-ethylstilbene.* Phenanthraquinone (0·9 g.) and α-ethylstilbene (0·7 g.) (Klages and Heilmann, *Ber.*, 1904, **37**, 1452) in 30 c.c. of benzene were exposed to sunlight for 13 days in December, the phenanthraquinone gradually dissolving completely. Then the contents of the tube were filtered, and the filtrate concentrated; a solid orange product (phenanthraquinone) appeared, which was filtered off. The filtrate was concentrated, and light petroleum (b. p. 50—70°) added until it became turbid. After 24 hours' standing, orange crystals of phenanthraquinone were formed; the filtrate from these, after addition of methyl alcohol and a few drops of acetone, yielded the photo-*product* (I*b*); colourless crystals, m. p. 169°, from light petroleum (b. p. 50—70°). When this was treated with concentrated sulphuric acid no colour occurred in the cold, but on being warmed on the water-bath, the acid became violet after a short time (Found: C, 86·7; H, 6·3. $C_{30}H_{24}O_2$ requires C, 86·6; H, 5·8%).

Thermal decomposition was carried out as described above for 30 minutes, and the products were α-ethylstilbene, which was purified by crystallisation from light petroleum (m. p. and mixed m. p.), and phenanthraquinone.

(iii) *With 1-phenyl-2-β-naphthylethylene.* Phenanthraquinone (0·4 g.) and 1-phenyl-2-β-naphthylethylene (0·4 g.) (Bergmann and Schapiro, *J. Org. Chem.*, 1947, **12**, 57) in benzene (30 c.c.) were exposed to sunlight for 15 days (April), the phenanthraquinone dissolving gradually. The contents of the tube were filtered and the filtrate concentrated. On addition of acetone, crystals were formed after some time in the ice-chest; the *product* (I*c*) recrystallised from chloroform–methyl alcohol as colourless crystals, m. p. 199° (orange melt) (Found: C, 87·6; H, 5·2. $C_{32}H_{22}O_2$ requires C, 87·6; H, 4·9%).

Thermal decomposition, as before, afforded phenanthraquinone and 1-phenyl-2-β-naphthylethylene (m. p. and mixed m. p.).

Photo-reactions of Stilbene.—(i) *With triketoindane.* Triketoindane (1 g.), stilbene (0·7 g.), and anhydrous sodium sulphate (0·5 g.) in benzene (25 c.c.) were exposed to sunlight for three weeks in February. The contents of the tube were filtered off, and the residue washed with water to remove sodium sulphate and unreacted triketone. The *product* (II) (0·6 g.) crystallised from benzene–petrol (b. p. 70—90°) as light yellow crystals, m. p. 210° (decomp.), easily soluble in benzene, difficultly soluble in cold alcohol and petrol, and not giving a colour reaction with 20% sodium hydroxide at room temperature, in contrast to the original ketone which gives an intense blue coloration with this reagent (Found: C, 80·4; H, 4·4. $C_{23}H_{16}O_3$ requires C, 81·2; H, 4·7%). Sodium sulphate was used in this experiment to retain any water which might enter the tube during sealing, as the ketone reacts rapidly with water to form the hydrate (" ninhydrin ").

Pyrolysis of (II) was carried out in a test-tube in a bath at 220° for 20 minutes; after cooling, the colourless crystals which had formed on the upper part of the test tube proved to be stilbene (m. p. and mixed m. p.).

(ii) *With* peri*naphthindane-7 : 8 : 9-trione.* The triketone (III) (1 g.) and stilbene (1 g.), partly dissolved and partly suspended in benzene (25 c.c.), were exposed to sunlight for 10 days (May). The reaction *product* (IV) which separated was crystallised from benzene–petrol (b. p. 70—90°) and then from methyl alcohol; m. p. 220—222° (decomp.; dark red-brown melt); yield 0·9 g. The pale yellow product is soluble in benzene and difficultly soluble in cold methyl and ethyl alcohol; it gives an orange colour with concentrated sulphuric acid and no colour reaction with 20% sodium hydroxide in the cold, in contrast to (III) which gives a blue coloration with this reagent (Found: C, 83·1; H, 4·6. $C_{27}H_{16}O_3$ requires C, 83·1; H, 4·7%).

Thermal decomposition of (IV) was carried out as in the case of (II) and stilbene was identified by m. p. and mixed m. p.

Photo-dimerisation of α-Naphthaquinone.—The quinone (0·5 g.) in benzene (12 c.c.) was exposed to sunlight (mid-November to mid-December); colourless crystals began to form after a week, and at the end of the experiment these were filtered off, washed with a little cold benzene, and crystallised from excess of alcohol; m. p. 244—248° (decomp.; brown melt) (Found: C, 75·7; H, 4·1. $C_{20}H_{12}O_4$ requires C, 75·9; H, 3·8%); yield 0·2 g. A parallel experiment carried out in the dark gave a negative result. The *dimer* is very difficultly soluble in hot benzene and boiling ether. It is insoluble in concentrated or dilute aqueous sodium hydroxide solution, and gives no colour reaction with concentrated sulphuric acid and no reaction with diazomethane.

The thermal decomposition of (V) was carried out in a large test-tube through which a stream of dry carbon dioxide passed. The lower part was heated at 270° for 10 minutes. The resulting brown melt was cooled and crystallised from ethyl alcohol, and the product proved to be α-naphthaquinone (mixed m. p. and properties). No other product could be detected.

Effect of sunlight on solid α-naphthaquinone. Solid α-naphthaquinone was exposed to sunlight in a Monax glass tube for two months (July and August) but no change could be observed. In a parallel experiment 2-methyl-1 : 4-naphthaquinone was transformed into the photo-dimer.

Behaviour of 2 : 3-Dimethyl-1 : 4-naphthaquinone in Sunlight.—The quinone (Fieser and Oxford, *J. Amer. Chem. Soc.*, 1942, **64**, 2063) was found to be stable when exposed to sunlight in benzene solution or in the solid state. These experiments were carried out as described above.

Molecular Weight of the Photo-dimer of 2-Methyl-1 : 4-naphthaquinone.—A determination carried out by Rast's method gave *M*, 357 (Calc. for $C_{22}H_{16}O_4$: *M*, 344).

Polymerisation of 1 : 2-*Benzanthracene in Sunlight.*—This substance (1 g.) (Eastman–Kodak) was dissolved in dry benzene (20 c.c.) and exposed to sunlight (January). After 24 hours' exposure, the colourless microcrystalline photo-*dimer* was obtained, and was recrystallised from tetralin at 100°. It is easily soluble in boiling tetralin, difficultly soluble in benzene and carbon disulphide; m. p. 235° (Found: C, 94·4; H, 5·6. $C_{36}H_{24}$ requires C, 94·7; H, 5·3%).

The photo-dimer (0·5 g.) was heated at 270° (ethyl phthalate bath) for 10 minutes in dry carbon dioxide and allowed to cool. The solidified melt proved to be the monomer (m. p. and mixed m. p.).

Polymerisation of 1 : 3-*Diphenylbenz*iso*furan in the Dark.*—This substance (0·2 g.) (Guyot and Catel, *loc. cit.*), contained in a sealed Pyrex tube, was completely immersed in boiling ethyl phthalate (270°) for 30 minutes; the tube was then rapidly chilled in ice–water. The contents of the tube were washed with hot light petroleum (b. p. 50—70°) several times (to remove any unchanged substance), and the insoluble residue dissolved in hot acetic acid (12 c.c. of 99·6% acid containing 0·5 c.c. of water); on slow cooling, colourless crystals were obtained and proved to be (VIII) (Guyot and Catel, *loc. cit.*) (m. p. and mixed m. p. and comparison of the properties) (Found: C, 88·8; H, 5·5. Calc. for $C_{40}H_{28}O_2$: C, 88·9; H, 5·2%); yield *ca.* 80%. If in the above experiment the reaction tube was allowed to cool very slowly, no dimeric product could be detected.

FACULTY OF SCIENCE, FOUAD I UNIVERSITY,
ABBASSIA, CAIRO, EGYPT.

[*Received, December 29th,* 1947.]

---

429. N¹-*Sulphanilamides derived from Aminoquinoxalines and Aminomethylquinoxalines.*

By BERTIE C. PLATT and THOMAS M. SHARP.

The three possible aminoquinoxalines, nine of the fifteen possible aminomethylquinoxalines, and nine of the corresponding N^1-sulphanilamides have been synthesised.

The identity of the product obtained from 2 : 3-diaminotoluene hydrochloride and mesoxalic ester has been established as 2-hydroxy-3-carbethoxy-5-methylquinoxaline.

A convenient method for the preparation of 3 : 5-dinitro-*o*-toluidine is described, and attention is drawn to a neglected method for the preparation of 3 : 5-dinitro-*p*-toluidine (Ullmann and Gross, *Ber.*, 1910, **43**, 2697).

IT has been reported (Schmith, *Dansk Tids. Farm.*, 1940, **14**, 215) that the seven isomeric sulphanilamidoquinolines have bacteriostatic activity against pneumococcus type I *in vitro* equal to that of sulphapyridine. It was thought that the isomeric sulphanilamidoquinoxalines—which stand in the same structural relationship to sulphanilamidopyrazine as do the sulphanilamidoquinolines to sulphapyridine—might be of chemotherapeutic interest, since favourable clinical reports of the use of sulphapyrazine have been published (*e.g.*, Ruegsegger, Hamburger, junr., Turk, Spies, and Blankenhorn, *Amer. J. Med. Sci.*, 1941, **202**, 432; Broh-Kahn and Erdman, *ibid.*, 1946, **212**, 170).

The effect of the introduction of a methyl group into the quinoxaline nucleus of sulphanilamidoquinoxalines has also been examined, since the presence and position of such an apparently inert group are known to cause profound changes in the biological activity of many types of compound, although at present no completely satisfactory explanations of these changes have been suggested. For example, 1 : 4-naphthaquinone has a slight vitamin-*K* activity which is increased 500-fold by the introduction of a methyl group into the 2-position (Dam, Glavind, and Karrer, *Helv. Chim. Acta*, 1940, **23**, 229), while a second methyl group in the 6-position results in an inactive compound (Fieser, Bowen, Campbell, Fry, and Gates, *J. Amer. Chem. Soc.*, 1939, **61**, 1927). The substitution of two methyl groups in the 1 : 9-positions of 2 : 8-diaminoacridine (proflavine) gives a compound with greatly enhanced antibacterial action (Albert, Rubbo, Goldacre, Davey, and Stone, *Brit. J. Exp. Path.*, 1945, **26**, 160). The effect of a change in position of the methyl groups is very marked in the riboflavin series. A shift of the methyl groups from the 6 : 7- to either the 5 : 7- or the 6 : 8-positions gives rise to inactive compounds (Kuhn, *Ber.*, 1937, **70**, 1293), but a shift to the 5 : 6-positions produces a compound which is an antagonist to the growth effect of riboflavin on rats (Emerson and Tishler, *Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 184). In the sulphonamide field, Läuger and Martin (*Schweiz. Med. Woch.*, 1943, **73**, 402) have shown that the 4-monomethyl derivative of N^1-benzoylsulphanilamide has a slight activity against experimental pneumococcal infections in mice, but the 3 : 4-dimethyl derivative (" Irgafen ") has a very high activity. Change of position of one of the methyl groups or the introduction of more methyl groups give rise to inactive compounds.

An instance of the enhancing effect of a methyl group on chemotherapeutic activity is provided in the present series of sulphanilamidoquinoxalines. It has been found by

Dr. G. Brownlee, of the Wellcome Physiological Research Laboratories, that N^1-(*3′-methyl-2′-quinoxalyl*)*sulphanilamide* is much more active against *Hæmophilus pertussis* infections of mice than N^1-(2′-quinoxalyl)sulphanilamide. It is also only about one-sixth as toxic.

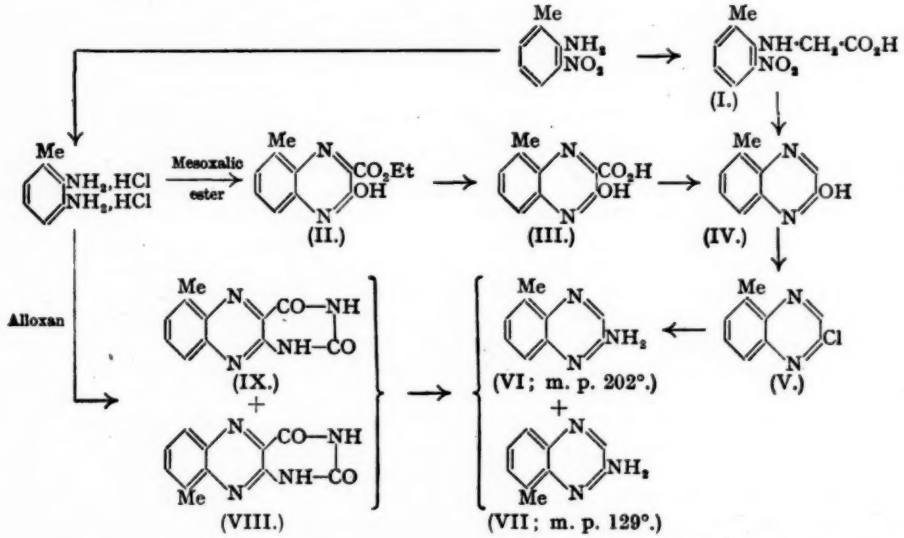
The sulphanilamidoquinoxalines were made either from the amine and acetylsulphanilyl chloride followed by hydrolysis of the N^4-acetyl group, or from the chloro-derivative and sulphanilamide. All were sparingly soluble in water.

The preparation of N^1-(2′-quinoxalyl)sulphanilamide was announced during the course of the present work by Weijlard, Tishler, and Erickson (*J. Amer. Chem. Soc.*, 1944, **66**, 1957), who obtained it from 2-aminoquinoxaline and acetylsulphanilyl chloride followed by deacetylation; it has now been found that this sulphonamide can be conveniently made in good yield by the interaction of 2-chloroquinoxaline (Gowenlock, Newbold, and Spring, *J.*, 1945, 622) with sulphanilamide in the presence of potassium carbonate and potassium iodide. The product diazotises and couples with alkaline β-naphthol; it is therefore N^1-(2′-quinoxalyl)sulphanilamide and not the isomeric N^4-(2′-quinoxalyl)sulphanilamide.

Similarly, interaction of 2-*chloro*-3-*methylquinoxaline* with sulphanilamide in the presence of potassium carbonate has given N^1-(3′-methyl-2′-quinoxalyl)sulphanilamide and not the isomeric N^4-(3′-methyl-2′-quinoxalyl)sulphanilamide. This was proved by the ability of the product to diazotise and couple and by its synthesis from 2-*amino*-3-*methylquinoxaline* and acetylsulphanilyl chloride, followed by deacetylation with alcoholic hydrochloric acid.

N^1-(*5′-Methyl-2′-quinoxalyl*)*sulphanilamide* has been prepared by two similar routes starting from 2-*amino*-5-*methylquinoxaline* (VI) and 2-*chloro*-5-*methylquinoxaline* (V). The latter was prepared from 2-*hydroxy*-5-*methylquinoxaline* (IV) which was obtained both from 2-*hydroxy*-3-*carbethoxy*-5-*methylquinoxaline* (II) and from N-(3-*nitro*-o-*tolyl*)*glycine* (I).

Although the reaction between 2 : 3-diaminotoluene hydrochloride and mesoxalic ester might have led to two isomeric hydroxy-carbethoxymethylquinoxalines, it did in fact give only one isomeride. This failure to give both isomeric products is of interest since 2 : 3-diaminotoluene hydrochloride gives the two isomeric products (VIII and IX) with alloxan; further, it has been shown that 3 : 4-diaminotoluene hydrochloride gives two isomerides with mesoxalic ester, alloxan (Platt, this vol., p. 1310) or ω-bromoacetophenone (Hinsberg, *Annalen*, 1887, **237**, 370; Lellmann and Donner, *Ber.*, 1890, **23**, 166). On the other hand, only one isomeride is formed from 3 : 4-diaminotoluene and monochloroacetone (Hinsberg, *loc. cit.*), oximinoacetone or methylglyoxal (von Pechmann, *Ber.* 1887, **20**, 2544). Moreover, only one isomeride is reported in each case from the interaction of 4 : 5-diamino-*m*-xylene or 3 : 4-diamino-*o*-xylene with alloxan (Stern and Holiday, *Ber.*, 1934, **67**, 1450).



The identity of the 2-hydroxy-5-methylquinoxaline (IV) has been established by its unambiguous synthesis from *N*-(3-nitro-*o*-tolyl)glycine (I). Pollak (*J. pr. Chem.*, 1915, **91**, 285), who investigated a series of reactions of chloro- and bromo-acetic acids with nitroamino-

toluenes, was unable to prepare this substituted glycine; it has now been obtained in 15% yield by heating 3-nitro-*o*-toluidine and bromoacetic acid at 125—140° with zinc chloride (absence of zinc chloride halves the yield).

2-Hydroxy-5-methylquinoxaline (IV) was converted *via* the 2-chloro-derivative (V) into 2-amino-5-methylquinoxaline (VI), m. p. 202°. This was identical with one of the two isomeric aminomethylquinoxalines obtained by treating a mixture of 5- and 8-methylalloxazines (IX and VIII) with concentrated sulphuric acid; the second isomeride (m. p. 129°) is most probably *2-amino-8-methylquinoxaline* (VII). The possibility exists that this product may be an inseparable mixture of 2-amino-8- and -5-methylquinoxaline since no independent synthesis of the former has been carried out.

It has not been found possible to synthesise N^4-acetyl-N^1-(8′-methyl-2′-quinoxalyl)-sulphanilamide from 2-amino-8-methylquinoxaline and acetylsulphanilyl chloride.

There are five possible monomethyl 5-aminoquinoxalines, of which only one, *viz.*, *5-amino-7-methylquinoxaline*, has been prepared. This exists as the monohydrate, as does also *5-aminoquinoxaline*; all the other amino- or aminomethyl-quinoxalines are anhydrous. 5-Amino-7-methylquinoxaline was synthesised from 3 : 5-dinitro-*p*-toluidine as starting material; this was readily obtained in quantity by the apparently neglected method of Ullmann and Gross (*Ber., loc. cit.*) by heating **p*-tosyl-*p*-toluidide with nitric acid under reflux. The more usual route of nitrating aceto-*p*-toluidide is unsatisfactory owing to the ease of removal of the acetyl group; tar formation follows from the presence of the then unprotected amino-group.

The only satisfactory method for the preparation of 3 : 5-dinitro-*o*-toluidine (required for the synthesis of *7-amino-5-methylquinoxaline*) described in the literature appeared to be that of McGookin (*J. Soc. Chem. Ind.*, 1941, **60**, 297) who commenced with *o*-cresol and obtained an overall yield of 85%, but a repetition of this method gave an overall yield of only 16%. It was found that 3 : 5-dinitro-*o*-toluidine could be conveniently prepared in good yield and in quantity by simply refluxing *p*-tosyl-*o*-toluidide successively with 25% and 35% nitric acid, followed by

TABLE I.

Preparation of N^1*-quinoxalylsulphanilamides from aminoquinoxalines and acetylsulphanilyl chloride.*

	N^4-Acetylsulphonamides.†							Sulphonamides.					
Amino-quin-oxalines.	M. p.	Solvent for recryst.	Analysis. Found, %. C.	H.	N.	S.	Method of hydro-lysis.	M. p.	Solvent for recryst.	Analysis. Found, %. C.	H.	N.	S.
5-Amino-	228—230°	Aq. EtOH	56·2	4·3	16·3	9·4	2·5% Aq. NaOH	163—165°	EtOH	—	—	18·6	10·7
6-Amino-	277 (dec.)	Aq. EtOH	56·2	4·1	16·6	9·6	5% Aq. NaOH	227—229	Aq. acetone	—	—	18·8	10·5
$C_{16}H_{14}O_3N_4S$ requires			56·1	4·1	16·4	9·4		$C_{14}H_{12}O_2N_4S$ requires				18·7	10·7
2-Amino-3-methyl-	—	—	—	—	—	—	Alc. HCl	207	HOAc	57·7	4·7	17·7	9·8
2-Amino-5-methyl-	—	—	—	—	—	—	Alc. HCl	202—204	C_6H_6	—	—	17·7	9·9
5-Amino-7-methyl-	209	$CHCl_3$	—	—	15·6	8·7	Alc. HCl	214—216	EtOH	57·4	4·7	18·1	10·9
6-Amino-2 (or 3)-methyl-	283—285	—	—	—	—	—	Alc. HCl	258	EtOH	57·7	4·6	17·8	10·7
7-Amino-6-methyl-	262—265	—	—	—	—	—	Alc. HCl	219—220	EtOH	57·4	4·5	18·2	10·2
7-Amino-5-methyl-	262	Aq. EtOH	—	—	15·6	—	Alc. HCl	225—227	PrⁱOH	57·5	4·4	18·2	10·2
$C_{17}H_{16}O_3N_4S$ requires					15·7	9·0		$C_{15}H_{14}O_2N_4S$ requires		57·3	4·5	17·8	10·2

† The N^4-acetylsulphonamides were prepared from the corresponding amine and acetylsulphanilyl chloride in dry pyridine.

hydrolysis of the crude nitration product. This gave 3 : 5-dinitro-*o*-toluidine in 68—91% overall yields from *p*-toluidine. It is to be noted that no nitro-group entered the "*p*-tosyl ring" under these conditions.

* *p*-Tosyl is used throughout for toluene-*p*-sulphonyl, except that new compounds are named systematically.

TABLE II.

Preparation of N¹-*quinoxalylsulphanilamides from 2-chloroquinoxalines and sulphanilamide.*

Chloro-quin-oxalines.	Conditions for prep.	Yield, %.	M. p.	Solvent for recryst.	Analysis. Found, %. C.	H.	N.	S.	Calc., %. C.	H.	N.	S.
2-Chloro- *	5 Hrs. at 165—175° + KI (0·1M) + K_2CO_3 (1M) + Cu in autoclave	82	250—252°†	Aq. dioxan	56·2	4·1	19·0	10·6	56·0	4·03	18·7	10·7
2-Chloro-3-methyl	12 Hrs. at 160—180° + K_2CO_3 (1M) + Cu in autoclave	63	207—209	$COMe_2$	57·7	4·7	17·7	9·8	57·3	4·5	17·8	10·2
2-Chloro-5-methyl	2½ Hrs. at 160—190° + KI (1M) + K_2CO_3 (1M) + Cu in autoclave	—	202—204	C_6H_6	—	—	17·7	9·9	57·3	4·5	17·8	10·2

* Gowenlock, Newbold, and Spring, *loc. cit.*

† Weijlard, Tishler, and Erickson, *loc. cit.*, obtained this compound by hydrolysis of the N^4-acetyl derivative and give m. p. 247—248°.

EXPERIMENTAL.*

2 : 3-, 3 : 4-, *and* 2 : 5-*Dinitroacetanilides.*—These were obtained by nitration of *m*-nitroacetanilide by modifications of the methods of Macciotta (*Ann. Chim. appl.*, 1939, **29**, 81) and Welsh (*J. Amer. Chem. Soc.*, 1941, **63**, 3276). A solution of *m*-nitroacetanilide (10 g.) in fuming nitric acid freed from nitrous acid (25 c.c.) was run into a well-stirred mixture of concentrated sulphuric acid (125 c.c.) and glacial acetic acid (25 c.c.), the temperature being kept between −10° and 0°. While the *m*-nitroacetanilide solution was being run in, a second similar solution was prepared and kept in the freezing mixture until required: this was repeated 5 times until a total of 50 g. of *m*-nitroacetanilide had been added. This procedure was necessary to prevent the latter from reacting with the nitric acid before its addition to the acetic–sulphuric acids (cf. Welsh, *loc. cit.*). After all the nitric acid solution had been added (50 mins.), stirring in the freezing mixture was continued for a further hour. The solution was *slowly* poured into stirred ice-water to give a pale yellow precipitate which was washed free from acid. If the addition to ice-water is carried out too quickly, a sticky mass is obtained which can be dealt with only by dissolution in acetic acid and repouring into water.

2 : 3-Dinitroacetanilide was obtained from this precipitate by crystallisation from benzene–acetone (2 : 1) in 31% yield (19·6 g.), m. p. 187°. 3 : 4-Dinitroacetanilide could be isolated from the more soluble fractions most conveniently by recrystallisation from chloroform, but this was unnecessary since the mixture of 3 : 4- and 2 : 5-dinitroacetanilides (34·4 g., 55%) was converted on hydrolysis and reduction into 1 : 2 : 4-triaminobenzene (used for 6-aminoquinoxaline preparation).

2 : 3-*Dinitroaniline.*—2 : 3-Dinitroacetanilide was hydrolysed with concentrated sulphuric acid at 110° (method of Wender, *Atti Reale Accad. Lincei*, 1889, **5**, I, 540; *Gazzetta*, 1889, **19**, 226).

1 : 2 : 3-*Triaminobenzene.*—2 : 3-Dinitroaniline (45 g.) was added in portions to a solution of stannous chloride (560 g.) in concentrated hydrochloric acid (750 c.c.). After the vigorous reaction had subsided, the solution was heated for 1½ hours on the water-bath, then cooled overnight in the refrigerator. The precipitate was freed from tin with hydrogen sulphide in weakly acid solution to give, on concentration, 1 : 2 : 3-triaminobenzene dihydrochloride (does not melt below 300°; 77—92% yields). The *dipicrate* was obtained as yellow crystals from water (decomp. 183°) (Found: C, 37·4; H, 2·78; N, 21·9. $C_6H_9N_3,2C_6H_3O_7N_3$ requires C, 37·2; H, 2·60; N, 21·7%).

5-*Aminoquinoxaline.*—Glyoxal "sulphate" (42 g.; K. Ott, D.R.-P. 362,743; 1922) was added in portions to a solution of 1 : 2 : 3-triaminobenzene dihydrochloride (25 g.) in aqueous sodium carbonate (800 c.c. of 10%) and the solution was refluxed for 1½ hours. After cooling, it was continuously extracted with ether; removal of the ether after drying (Na_2SO_4) gave the required base, m. p. 85—86° (16·8 g., 81%). Recrystallisation from light petroleum (b. p. 40—60°) gave pale yellow plates, m. p. 87—88°, of the *monohydrate* (Found: C, 59·1; H, 5·54; N, 26·2. $C_8H_7N_3,H_2O$ requires C, 58·9; H, 5·56; N, 25·7%). On drying at 75° in a vacuum it lost 11·5% of its weight ($C_8H_7N_3,H_2O$ requires loss, 11·0%) to give the pale orange anhydrous *base*, m. p. 93—95° (Found: C, 66·3; H, 5·1; N, 28·5. $C_8H_7N_3$ requires C, 66·2; H, 4·86; N, 28·9%), which reverts to the paler monohydrate on exposure to air.

Note on Preparation of **5-** *and* **6-*Aminoquinoxalines.***—Instead of separating the isomerides obtained in the nitration of *m*-nitroacetanilide (above) and acting on them separately with glyoxal, the mixture of 2 : 3-, 3 : 4-, and 2 : 5-dinitroanilines can be reduced to the mixed triaminobenzenes and treated with glyoxal. The resulting 5- and 6-aminoquinoxalines were readily separated by extraction with light petroleum, in which the 6-isomeride is insoluble.

6-Aminoquinoxaline was obtained in 79% yield, m. p. 157° (Hinsberg, *Ber.*, 1886, **19**, 1253, gives m. p. 158—159°).

2-Hydroxy-3-methylquinoxaline (Hinsberg, *Annalen*, 1896, **292**, 249), m. p. 245°, was obtained in 77% yield from *o*-phenylenediamine and pyruvic acid in alcoholic solution (Found: C, 67·3; H, 5·1. Calc. for $C_9H_8ON_2$: C, 67·4; H, 5·0%).

2-*Chloro-3-methylquinoxaline.*—Phosphorus oxychloride (600 c.c.) was heated under reflux with 2-hydroxy-3-methylquinoxaline (60 g.) for ¾ hour. The solution was poured cautiously into stirred

* *Added in Proof.*—A paper by Wolf, Bentel, and Stevens (submitted February 24th, 1948) has just appeared (*J. Amer. Chem. Soc.*, 1948, **70**, 2572) in which eight of the compounds recorded here as new are also described.

ice-water and made alkaline with sodium hydroxide solution. The precipitated *2-chloro-3-methylquinoxaline* (m. p. 83—87°; 57 g., 85%) after recrystallisation from light petroleum or sublimation in a vacuum gave colourless needles, m. p. 87° (Found: Cl, 19·9. $C_9H_7N_2Cl$ requires Cl, 19·9%). It is readily soluble in organic solvents.

2-Amino-3-methylquinoxaline.—A solution (300 c.c.) of dry ammonia in absolute alcohol, saturated at 0°, and 2-chloro-3-methylquinoxaline (13·4 g.) were heated in an autoclave for 7 hours at 160—175°. After removal of the alcohol, the solid was washed with cold water and extracted with hot water to give, on cooling, very pale yellow needle clusters of *2-amino-3-methylquinoxaline*, m. p. 163—165° (6·4 g., 54%) (Found: C, 68·2; H, 6·1; N, 25·9. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). The base can be sublimed in a vacuum and is moderately soluble in organic solvents, but sparingly soluble in hot carbon tetrachloride and in light petroleum.

3-Nitro-*o*-toluidine was prepared by nitration of aceto-*o*-toluidide by Cohen and Dakin's method (*J.*, 1901, **79**, 1127), but the hydrolysis of the resulting mixed nitroacetotoluidides and separation of the 3-nitro- and 5-nitro-*o*-toluidines was carried out according to Gabriel and Thieme (*Ber.*, 1919, **52**, 1080). This gave yields of 45—66% of 3-nitro- and 27—15% of 5-nitro-base.

5- and 8-Methylalloxazines.—Concentrated hydrochloric acid (730 c.c.) was cautiously added during 1 hour to a suspension of 3-nitro-*o*-toluidine (66 g.) and iron filings (110 g.) in water (440 c.c.). The mixture was heated on the water-bath for ½ hour and filtered hot from unreacted iron, and a hot solution of alloxan (70 g.) and boric acid (58 g.) in water (580 c.c.) was added to the filtrate. Within a few minutes a yellow precipitate separated; after 1 hour's heating on the water-bath, water (4 l.) was added, and the yellowish-green mixture of 5- and 8-methylalloxazines (decomp. 315—325°; 50 g., 50%) filtered off. These were separated by fractional crystallisation from acetic acid; the less soluble fractions yielded 8-methylalloxazine, m. p. 298° (Found: C, 57·1; H, 3·78; N, 23·5. Calc. for $C_{11}H_8O_2N_4$: C, 57·8; H, 3·53; N, 24·5%) (cf. Karrer and Musante, *Helv. Chim. Acta*, 1935, **18**, 1140), and from the more soluble fractions there was obtained *5-methylalloxazine*, decomp. 332° (Found: C, 57·7; H, 3·73; N, 23·7%). The latter is contaminated with a small proportion of its 8-isomeride, since on treatment with concentrated sulphuric acid (see below) it gave a small amount of 2-amino-8-methylquinoxaline together with the main product, 2-amino-5-methylquinoxaline.

2-Amino-8-methylquinoxaline.—8-Methylalloxazine (2 g.) was treated with concentrated sulphuric acid (14 c.c.) at 230—240° for 10 mins.; the solution was poured into water, made alkaline with sodium hydroxide, and the product isolated by continous extraction with ether. After recrystallisation from light petroleum (b. p. 60—80°) *2-amino-8-methylquinoxaline* was obtained in very pale yellow crystals, m. p. 129° (Found: C, 67·2; H, 5·9; N, 25·9. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). The base is soluble in organic solvents and can be sublimed.

2-Amino-5-methylquinoxaline.—(*a*) The mixed crude 5- and 8-methylalloxazines (37 g.) were treated as above with concentrated sulphuric acid. The residue from the ethereal extracts was recrystallised from benzene to yield very pale yellow crystals of *2-amino-5-methylquinoxaline*, m. p. 201—202°, identical with that obtained in (*b*) (Found: C, 67·9; H, 5·9; N, 25·7%). 2-Amino-8-methylquinoxaline was obtained from the more soluble benzene fractions and purified by recrystallisation from light petroleum. The total yield of 2-amino-5- and -8-methylquinoxalines was 4·0 g. (16%).

(*b*) A solution (50 c.c.) of dry ammonia in absolute alcohol, saturated at 0°, and 2-chloro-5-methylquinoxaline (see below; 3 g.) were heated in an autoclave at 145—160° for 15 hours. After evaporation, the residue was extracted with hot light petroleum, and the insoluble portion recrystallised from benzene to yield 2-amino-5-methylquinoxaline, m. p. 202° (1·0 g.), identical with that from (*a*) above.

2-Chloro-5-methylquinoxaline.—2-Hydroxy-5-methylquinoxaline (see below; 5 g.) was heated under reflux with phosphorus oxychloride (50 c.c.) for ¾ hour. The cooled red solution was cautiously poured on ice and finally made alkaline to precipitate a solid, which was crystallised from light petroleum or sublimed in a vacuum to give colourless needles of *2-chloro-5-methylquinoxaline*, m. p. 95° (3·1 g., 56%) (Found: C, 60·2; H, 3·78; N, 16·0; Cl, 19·9. $C_9H_7N_2Cl$ requires C, 60·5; H, 3·95; N, 15·7; Cl, 19·9%).

2-Hydroxy-5-methylquinoxaline.—(*a*) *N*-(3-Nitro-*o*-tolyl)glycine (see below; 5 g.) was treated with concentrated hydrochloric acid (25 c.c.) and tin (5 g.). After completion of the reaction on the water-bath (1 hr.), the solution was diluted, freed from tin, and finally concentrated, whereupon it became pink and deposited a precipitate. Sublimation in a vacuum gave colourless needles of *2-hydroxy-5-methylquinoxaline*, m. p. 286° (Found: C, 67·6; H, 5·1. $C_9H_8ON_2$ requires C, 67·5; H, 5·0%).

(*b*) 2-Hydroxy-5-methylquinoxaline-3-carboxylic acid (5 g.; see below) was heated at 230—245° for ½ hr. The crude product (3·7 g., 95%) on recrystallising from benzene gave 2-hydroxy-5-methylquinoxaline, m. p. 286° (Found: C, 67·6; H, 4·9; N, 17·1%), identical with that in (*a*). This quinoxaline is insoluble in water, slightly soluble in acetone and carbon tetrachloride, more soluble in alcohol, ether, and ethyl acetate and crystallises well from benzene.

N-(3-Nitro-o-tolyl)glycine.—Monobromoacetic acid (47·7 g.; 1 mol.), 3-nitro-*o*-toluidine (101·7 g.; 2 mols.), and zinc chloride (9 g.) were heated together at 125—140° for 3 hours. The red mass, obtained after pouring into water, was extracted several times with hot sodium carbonate solution (leaving a residue of recovered 3-nitro-*o*-toluidine); the combined extracts were acidified, and the precipitate recrystallised from carbon tetrachloride to give scarlet needles of *N-(3-nitro-o-tolyl)glycine*, m. p. 135° (gas evolution at 175°) (10·5 g.; 15% yield calc. from bromoacetic acid) (Found: C, 51·9; H, 4·79; N, 13·1. $C_9H_{10}O_4N_2$ requires C, 51·4; H, 4·79; N, 13·3%).

2-Hydroxy-3-carbethoxy-5-methylquinoxaline.—Iron filings (180 g.) were added in portions to a suspension of 3-nitro-*o*-toluidine (100 g.) in concentrated hydrochloric acid (600 c.c.); after completion of the reaction on the water-bath (½ hr.), water (600 c.c.) was added, unreacted iron removed, and a solution of diethyl mesoxalate monohydrate (100 g.; *Org. Synth.*, Coll. Vol. I, 1941, p. 266) in water (800 c.c.) was added. A precipitate formed at once and after one hour on the water-bath it was filtered off, washed with water, and dried (101 g., 66%). After recrystallisation from carbon tetrachloride, *2-hydroxy-3-carbethoxy-5-methylquinoxaline* formed pale yellow needles, m. p. 225° (Found: C, 62·1; H, 5·50; N, 12·1. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·21; N, 12·1%). The ester is soluble in most organic solvents, but is insoluble in light petroleum and in cold water.

2-Hydroxy-5-methylquinoxaline-3-carboxylic Acid.—The foregoing ester (105·5 g.) was hydrolysed by heating with sodium hydroxide solution (900 c.c. of 10%) on the water-bath for 1 hr. Acidification yielded the *methyl acid* (93 g., 100%), m. p. 230° (with loss of carbon dioxide) (Found: C, 58·8; H, 4·3; N, 14·0. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 4·0; N, 13·7%). The acid is insoluble or sparingly soluble in most organic solvents and crystallises from 50% acetic acid in yellow prisms.

3 : 5-*Dinitro*-p-*toluidine.*—The method of Ullmann and Gross (*loc. cit.*) was found to be very convenient, giving overall yields from *p*-toluidine of 51% on large batches. It has been confirmed that the more usual nitration of aceto-*p*-toluidide cannot be effected on larger than 20—25 g. batches (Niementowski, *Ber.*, 1886, **19**, 717; Brady, Day, and Rolt, *J.*, 1922, **121**, 527).

5-Amino-7-methylquinoxaline.—3 : 5-Dinitro-*p*-toluidine (30 g.) and iron filings (90 g.) were suspended in hot alcohol (500 c.c.) and concentrated hydrochloric acid (90 c.c.) was added in small portions. After the vigorous reaction had subsided, the mixture was refluxed for one hour, and the alcohol distilled off. Addition of sodium carbonate solution and filtration gave an aqueous solution of 3 : 4 : 5-triaminotoluene. Glyoxal bisulphite (40 g.) was added, and the solution heated for one hour on the water-bath; yellow-brown crystals separated within a few minutes and later redissolved. After cooling, the crude base was filtered off and extracted with benzene to give *5-amino-7-methylquinoxaline monohydrate* (10 g., 37% overall yield from 3 : 5-dinitro-*p*-toluidine), yellow needles, m. p. 122° (with steam evolution), which after cooling remelt at 103° (Found: C, 61·2; H, 6·22; N, 23·8. $C_9H_9N_3,H_2O$ requires C, 61·0; H, 6·26; N, 23·7%. Found: loss at 60°/25 mm., 10·0. $C_9H_9N_3,H_2O$ requires loss, 10·2%). The anhydrous *base* melts at 103° (Found: C, 67·3; H, 5·9. $C_9H_9N_3$ requires C, 67·9; H, 5·7%); on exposure to air it readily reverts to the monohydrate. It is soluble in the common warm organic solvents and crystallises in yellow needles from light petroleum or water; it can be sublimed in a vacuum.

2(or 3)-*Methyl-6-aminoquinoxaline.*—A solution of methylglyoxal (18·4 g.; Riley, Morley, and Friend, *J.*, 1932, 1875) in water (70 c.c.) was added to a solution of 1 : 2 : 4-triaminobenzene dihydrochloride (50 g.) in aqueous sodium carbonate solution (10%; 500 c.c.) and heated for ½ hour on the water-bath; a yellow-green solid was precipitated. This was recrystallised from carbon tetrachloride to give the *base* (19·7 g., 49%) as yellow crystals, m. p. 172°, raised to 173° by passing its benzene solution through alumina (Found: C, 68·5; H, 5·90; N, 26·0. $C_9H_9N_3$ requires C, 67·9; H, 5·70; N, 26·4%). This base can be sublimed in a vacuum; it is readily soluble in acetone and alcohol, moderately soluble in hot benzene and hot water, readily soluble in hot chloroform and ethyl acetate, and very sparingly soluble in hot ether.

5-Nitro-2 : 4-diaminotoluene.—5-Nitro-2 : 4-bisacetamidotoluene (102 g.; Maron and Salsberg, *Ber.*, 1911, **44**, 3004) was heated with concentrated sulphuric acid (204 c.c.) on the water-bath until a clear solution resulted (1—2 hours). This was poured on ice-water, made alkaline, and the precipitated 5-nitro-2 : 4-diaminotoluene, m. p. 152° (41·3 g., 61%), filtered off.

7-Amino-6-methylquinoxaline.—Sodium hydrosulphite (dithionite) (100 g.) was added to a suspension of 5-nitro-2 : 4-diaminotoluene (34·2 g.) in warm 50% alcohol (960 c.c.). After completion of the reduction, a solution of glyoxal bisulphite (46·5 g.) in water (700 c.c.) was added, and the whole heated on the water-bath for 2 hours. Addition of alkali precipitated *7-amino-6-methylquinoxaline*, pale orange crystals from benzene, m. p. 194—195° (24·7 g., 76%) (Found: C, 68·1; H, 6·1; N, 25·8. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). The base is readily soluble in cold acetone, alcohol, chloroform, and ethyl acetate, soluble in hot benzene, carbon tetrachloride, ether, and water, and insoluble in light petroleum.

3 : 5-*Dinitro*-o-*toluidine.*—*p*-Tosyl-*o*-toluidide (85·6 g.) was heated under reflux with nitric acid (240 c.c., 25% w/v) until the solid melted to a red oil and resolidified (12 mins.); concentrated nitric acid (38 c.c.; to give a 35%w/v solution) was added, and heating continued for 1½ hours. After cooling, the supernatant liquid was decanted, the residue was ground under water, filtered off, washed free from acid (this is essential), and dried to give the crude 3 : 5-*dinitro-2-toluene*-p-*sulphontoluidide* (97 g., m. p. 145—150°). Recrystallisation from alcohol or benzene gave buff-coloured crystals, m. p. 161—163° (Found: C, 48·0; H, 4·3; N, 12·0; S, 9·2. $C_{14}H_{13}O_6N_3S$ requires C, 47·9; H, 3·7; N, 12·0; S, 9·1%).

Direct reaction of *p*-tosyl-*o*-toluidide with 36% w/v nitric acid gave only a poor yield, while the use of 25% nitric acid alone gave mainly 5-nitro-2-*p*-tosyltoluidide, m. p. 174—175° (lit. m. p. 174°) (Found C, 54·6; H, 4·80; N, 9·4; S, 10·3. Calc. for $C_{14}H_{14}O_4N_2S$: C, 54·9; H, 4·61; N, 9·2; S, 10·5%).

Hydrolysis of the 3 : 5-dinitro-compound (97 g.) with concentrated sulphuric acid (265 c.c.) at 110° for 10 mins. gave 3 : 5-dinitro-*o*-toluidine (52 g., 81% overall yield) (Found: N, 21·2. Calc. for $C_7H_7O_4N_3$: N, 21·3%), m. p. 211—213°, identical with a sample made by McGookin's method (*loc. cit.*).

7-Amino-5-methylquinoxaline.—3 : 5-Dinitro-*o*-toluidine (5 g.) was suspended in water (60 c.c.) and sodium hydrosulphite (dithionite) (38 g.) added; a vigorous reaction ensued which was finally completed on the water-bath. After the mixture had been made just alkaline, glyoxal bisulphite (6·7 g.) in water (50 c.c.) was added, and the whole heated for 1 hr. on the water-bath. Addition of sodium hydroxide solution to the cooled solution precipitated a yellow solid, m. p. 157—160° (1·2 g., 30%). After purification of its benzene solution through alumina, *7-amino-5-methylquinoxaline* was obtained in yellow crystals, m. p. 158—160° (Found: C, 68·2; H, 5·77; N, 25·7. $C_9H_9N_3$ requires C, 67·9; H, 5·69; N, 26·4%). It is very soluble in cold acetone and glacial acetic acid, moderately soluble in cold ether and ethyl acetate, sparingly soluble in cold benzene and chloroform, and soluble in hot carbon tetrachloride or water.

The authors thank Messrs. D. Latham and C. J. Keattch for assistance with the experimental work. Microanalyses were carried out by Mr. J. McMurray of the Wellcome Chemical Works, Dartford, and by Drs. Weiler and Strauss, Oxford.

WELLCOME LABORATORIES OF TROPICAL MEDICINE,
183, EUSTON ROAD, N.W. 1.

[*Received, January 14th*, 1948.]

430. *Chemistry of the Inter-halogen Compounds. Part I. The Reaction of Bromine Trifluoride with Metallic Halides.*

By A. G. Sharpe and H. J. Emeléus.

Bromine trifluoride converts many metallic chlorides, bromides, and iodides into fluorides. Treated with excess of the reagent, the chlorides of potassium, silver, and barium yield the *bromofluorides* (*bromotetrafluorides*) $KBrF_4$, $AgBrF_4$, and $BaBr_2F_8$. Indications of the formation of other polyhalides of this type have been obtained.

Bromine trifluoride was first prepared more than forty years ago (Lebeau, *Compt. rend.*, 1905, **141**, 1015; Prideaux, *J.*, 1906, **89**, 316), but few details of its reactions with inorganic compounds have been published. A wide range of preliminary experiments with liquid bromine trifluoride showed that the compound was highly reactive. The study of its interaction with metallic halides is one of the simplest cases, particularly as the possibility of oxyfluoride formation can be excluded. The halides of lithium, sodium, potassium, rubidium, cæsium, copper, silver, calcium, strontium, barium, cadmium, aluminium, thallium, lead, uranous uranium, cobalt, and ferric iron have been examined.

The products of reaction, obtained in each case by treating the halide with excess of bromine trifluoride and pumping off the excess volatile material, were of several types. Cadmium iodide and lithium chloride, typical halides of elements of constant valency, gave the corresponding fluorides, which were not appreciably soluble in liquid bromine trifluoride. Anhydrous aluminium and ferric chlorides reacted similarly, but only very slowly and incompletely. Cuprous, thallous, plumbous, and cobaltous chlorides, and plumbous bromide, halides of elements of variable valency, gave mixtures of the lower and the higher fluorides, which were also not noticeably soluble in bromine trifluoride. Probably coating effects prevented complete conversion into the higher fluoride. Uranium tetrafluoride was completely converted into the volatile hexafluoride, and similar complete conversion will probably be found for halides of other elements, *e.g.*, vanadium, molybdenum, and tungsten, which form volatile highest fluorides. The chlorides of potassium, silver, and barium reacted with bromine trifluoride in the normal manner, free chlorine and bromine being formed (*e.g.*, $3KCl + BrF_3 = 3KF + Br + 3Cl$), but part of the excess bromine trifluoride was not removable in a high vacuum. Compounds having the respective empirical formulæ $KBrF_4$, $AgBrF_4$, and $Ba(BrF_4)_2$ were formed; their nature is discussed below.

Potassium bromofluoride (*bromotetrafluoride*), $KBrF_4$, the most closely studied of the new compounds, is a white crystalline solid which loses bromine trifluoride on heating, the more electronegative halogen remaining with the metal. This parallels the thermal decomposition of potassium iodochloride, $KICl_4$ (Caglioti and Centola, *Gazzetta*, 1933, **63**, 907), and rubidium monofluorotrichloroiodide, $RbFICl_3$ (Booth, Swinehart, and Morris, *J. Amer. Chem. Soc.*, 1932, **54**, 2561), to potassium chloride and rubidium fluoride, respectively. When heated in a platinum crucible, the crucible is attacked by potassium bromofluoride and addition of water to the solid product results in the deposition of the sparingly soluble potassium hexafluoroplatinate, a method of preparation which is probably more convenient than that of Schlesinger and Tapley (*ibid.*, 1924, **46**, 276) involving the action of the complex fluoride $3KF,HF,PbF_4$ on platinum, and the subsequent removal of lead.

With water, potassium bromofluoride decomposes rapidly, but much less violently than bromine trifluoride. The products are bromine, bromic acid, hydrofluoric acid, and oxygen. The first stage of the reaction is probably $BrF_4^- + 2H_2O \longrightarrow HBrO_2 + 3H^+ + 4F^-$ (cf. $BrF_3 + 2H_2O \longrightarrow HBrO_2 + 3H^+ + 3F$), followed by decomposition of the bromous acid to bromine, bromic acid, and oxygen. Further reactions of bromofluorides, expecially as fluorinating agents, are being studied in detail.

The proposed formulation of the polyhalide as $K^+(BrF_4)^-$ is supported by analogy with $KICl_4$, shown by Mooney (*Z. Krist.*, 1938, **98**, 377) to contain K^+ and planar ICl_4^- ions. Powder *X*-ray photographs of $KBrF_4$ show no lines due to potassium fluoride, but instead an entirely different set of lines. There are great differences in reactivity between potassium bromofluoride and bromine trifluoride. The latter, for example, reacts vigorously with carbon tetrachloride and explodes with acetone or dioxan, whereas the potassium compound neither reacts nor dissolves. Even boiling bromine trifluoride (b. p. 128°) has no action on platinum, which the potassium compound attacks readily on heating. The reactivity of the silver and barium compounds is rather greater, perhaps because the bromine trifluoride dissociation pressures of these compounds are greater than that of the potassium salt. They do not react with carbon

tetrachloride, but ignite ethyl ether, acetone, dioxan, and petrol. The existence of a silver polyhalide but not of a corresponding thallous compound is interesting in that the existence of silver tri-iodide (Schmidt, *Z. anorg. Chem.*, 1895, **9**, 418) is rather doubtful, whereas thallous tri-iodide (Wells and Penfield, *Z. anorg. Chem.* 1894, **6**, 312) is well characterised, being isomorphous with the tri-iodides of rubidium and cæsium. The final point supporting the existence of the bromofluoride ion $(BrF_4)^-$ is the combination of two such units with the invariably bivalent barium ion.

The $(BrF_4)^-$ ion may also be invoked to explain the electrical conductivity observed in pure liquid bromine trifluoride (unpublished observations by A. A. Banks and A. Woolf). The specific conductivity is 8×10^{-3} at 25°, and may perhaps be explained by the existence in the solid and liquid of ions BrF_2^+ and BrF_4^-. Chlorine trifluoride, which apparently does not form polyhalides analogous to $KBrF_4$ and $KICl_4$, has zero conductivity in the liquid state; iodine pentafluoride has a much lower conductivity (κ = approx. 10^{-5} at 25°). Solutions of potassium fluoride in bromine trifluoride are better conductors than the pure solvent.

If it is assumed that the BrF_4^- ion has a configuration similar to that of ICl_4^-, and the covalent radii for bromine and fluorine are 1·14 A. and 0·64 A., respectively, the Br–F distance should be 1·8 A. and the ion would therefore be considerably smaller than the ICl_4^- ion, in which the I–Cl distance is 2·34 A.

The existence of bromofluorides other than those of potassium, silver, and barium is extremely likely, but the possibility of isolating them in a pure state by the technique of pumping off bromine trifluoride will depend on the dissociation pressures of the compounds; and no solvent suitable for the recrystallisation of bromofluorides or for the separation of mixtures of fluoride and bromofluoride has yet been found. The chlorides of sodium, rubidium, cæsium, calcium, and strontium are rapidly converted by bromine trifluoride into fluorides, soluble, like those of potassium, silver, and barium, in excess of the reagent; and although the ratios of bromine trifluoride to metallic fluoride in the solid products obtained are other than 1 : 1 and 2 : 1, there is ample evidence for some sort of compound formation. Formation of lattice compounds containing fluoride and bromofluoride ions, as well as of mixtures, is possible, and a further study of these products by *X*-ray methods and the measurement of dissociation pressures may elucidate this point.

Iodine pentafluoride is a much less vigorous fluorinating agent than the bromine compound, but preliminary experiments have shown that it dissolves potassium fluoride and probably forms a compound KIF_6. Chlorine trifluoride, on the other hand, converts other halides into fluorides only, *e.g.*, potassium bromide and silver chloride yield potassium fluoride and silver bifluoride respectively, and no evidence for compound formation between chlorine trifluoride and metallic fluorides has been obtained.

Experimental.

Bromine trifluoride was prepared by a method similar to that of Ruff and Braida (*Z. anorg. Chem.*, 1932, **206**, 62). Reaction between bromine vapour, carried in a stream of nitrogen, and fluorine took place in a copper T-tube; the product was collected in a copper trap cooled by immersion in water. The crude bromine trifluoride was purified by distillation in a steel retort, the fraction boiling at 126—128° being collected separately and stored in a steel bottle stoppered by a screw-on steel cap. Immediately before use, the reagent was redistilled in quartz under reduced pressure at room temperature in order to free it from small quantities of ferric fluoride produced by slight attack on the containing vessel.

Reactions were carried out by slow addition of a large excess of bromine trifluoride to the halide in a quartz flask. When the reaction (if any) had subsided, the flask and its contents were heated to approx. 120° for a few minutes, and allowed to cool. The flask was then connected by a quartz trap cooled in liquid air to a simple vacuum line. The excess of bromine trifluoride was pumped off in a vacuum, without external heating, and condensed in the trap; distillation was continued until a very nearly constant weight was attained. In such a series of operations the loss in weight of the quartz reaction vessel was negligibly small (about 0·01%—a few mg. on 30 g.) so long as the apparatus was quite dry, and the formation of hydrogen fluoride thereby avoided. As a lubricant for ground joints, a very thin film of silicone vacuum grease was used; in bulk, this reacts explosively with bromine trifluoride, and the amount used was kept at the absolute minimum consistent with maintenance of a vacuum.

Potassium Bromofluoride (*Bromotetrafluoride*).—Approx. 0·5 g. of dried A.R. potassium chloride was caused to react as described above; chlorine was evolved. Values obtained for the conversion factor KCl : product indicated an equivalent weight of 193 ($KBrF_4$ requires 195). The product was analysed for (i) potassium, by exposure to moist air, followed by conversion into sulphate; (ii) bromine, by decomposition in a stoppered bottle with dilute ammonia, reduction with sulphur dioxide, and precipitation as silver bromide; (iii) fluorine, by decomposition with dilute ammonia and estimation as calcium fluoride (Treadwell and Hall, "Analytical Chemistry," Vol. II, 9th English edtn., p. 397) (Found: K, 20·7; Br, 39·5; F, 39·7. $KBrF_4$ requires K, 20·0; Br, 41·0; F, 39·0%). Discrepancy with calculated results is attributed to the presence of about 2% of potassium fluoride in the product. The *compound* was also prepared by direct combination of potassium fluoride and bromine trifluoride; the simple halide dissolved with no sign of reaction beyond a slight evolution of heat. The ratios found for KF : BrF_3 in two

preparations were 1·00 : 0·98 and 1·00 : 0·99. With potassium bromide and iodide vigorous reactions took place, clouds of bromine being evolved in the former reaction; most of the iodine from the iodide appeared to be fluorinated before it escaped. In each case the product was qualitatively identical with that obtained from the chloride or fluoride, but the reactions were too violent, and attack on the reaction vessel too marked, for quantitative study.

Silver Bromofluoride (*Bromotetrafluoride*).—This *compound* was prepared by treating either argentous fluoride or chloride with bromine trifluoride. The fluoride dissolved without any sign of reaction; chlorine was liberated from the chloride. The product after excess of reagent had been pumped off was white, and could therefore have contained no significant quantity of argentic fluoride, which is black. Gravimetric conversion factors from argentous fluoride and chloride indicated equivalent weights of 259 and 262 respectively ($AgBrF_4$ requires 264).

Decomposition with sulphurous acid reduced all the bromine to bromide, and after addition of a slight excess of silver nitrate solution and acidification with nitric acid, silver bromide equivalent to bromine in the compound was filtered off and weighed. For the determination of silver and fluorine, a fresh sample was decomposed with sodium carbonate solution containing a little potassium bromide; the solution was made weakly acid with nitric acid, and silver bromide, this time equivalent to silver, was filtered off; fluoride was determined in the filtrate by the method cited above. The use of sulphur dioxide was avoided in order to prevent co-precipitation of calcium sulphate with calcium fluoride (Found: Ag, 40·6; Br, 30·0; F, 27·3. $AgBrF_4$ requires Ag, 40·9; Br, 30·3; F, 28·0%).

Barium Bromofluoride (*Bromotetrafluoride*).—This salt was prepared in the same way, by treating anhydrous barium chloride with bromine trifluoride. The weight equivalent to $BaCl_2$ was 445 (duplicate) ($BaBr_2F_8$ requires 449). Barium was determined by conversion into fluoride and then into sulphate by heating to constant weight with concentrated sulphuric acid. Decomposition with sodium carbonate solution, removal of all barium as carbonate, and reduction by sulphur dioxide solution was followed by precipitation of the bromine as silver bromide. Barium fluoride is somewhat soluble in water, and for the determination of fluorine the barium bromofluoride was decomposed by dilute ammonia, and then sufficient water was added to dissolve all the barium fluoride; barium was precipitated as carbonate, and fluoride estimated (as above) in the filtrate (Found: Ba, 32·1; Br, 35·2; F, 31·2. $BaBr_2F_8$ requires Ba, 30·5; Br, 35·7; F, 33·9%). Attempts to prepare *barium bromofluoride* from barium fluoride gave products of approximate composition $BaF_2,0·9BrF_3$ and $BaF_2,1·1BrF_3$ in successive experiments; their nature is still being investigated; it is considered most likely that they are mixtures of roughly equal quantities of BaF_2 and $Ba(BrF_4)_2$.

Reaction of Bromine Trifluoride with Other Metal Halides.—Lithium chloride gave lithium fluoride, containing only a trace of chlorine or bromine. Lithium fluoride was not appreciably soluble in bromine trifluoride and was recovered unchanged in weight and free from bromine. Cadmium iodide yielded pure cadmium fluoride. When sodium chloride was treated in a platinum crucible, and excess of the reagent removed by gentle heating, the residue was sodium fluoride (Found: Na, 54·4; F, 44·8; Cl, Br, nil; equiv., 41·8. Calc. for NaF: Na, 54·7; F, 45·3%; equiv., 42·0). When, however, the reaction was carried out as in the preparation of potassium bromofluoride, products of widely variable composition containing sodium, bromine, and fluorine resulted. Sodium bromide and iodide reacted similarly. Sodium fluoride dissolved in bromine trifluoride and a product $NaF,0·97BrF_3$ was obtained. This was probably impure sodium bromofluoride, $NaBrF_4$. It was insoluble in, and did not react with, organic solvents; it oxidised potassium iodide solution with the formation of considerably less than the expected quantity of free iodine. This compound was rapidly decomposed to sodium fluoride and bromine trifluoride at 80°. Comparison of the % losses in weight by the sodium and potassium compounds on heating 0·5-g. samples for 5 mins. at 200° illustrates the much lower stability of the former: the potassium compound lost only 30% by weight, but the sodium compound was completely decomposed into sodium fluoride. Calcium, cæsium, and rubidium chlorides, and calcium and strontium fluorides, gave ill-defined products, the bromine content of which varied with the temperature and time of evacuation. Here again it is highly probable that unstable compounds were formed, and that retention of bromine trifluoride was not mechanical, for though stoicheiometrically indefinite, the products possessed the same degree of reactivity as the definite bromofluorides. The high reactivity of bromine trifluoride and the considerable reactivity of the polyhalides make the quantitative study of loss of bromine trifluoride from them rather complicated, but suitable techniques are being developed. The indications so far are that bromofluorides of varying stability are formed only by the alkali metals (excluding lithium), the alkaline earths, and silver. This is borne out by further tests with other metal halides, which are described briefly below.

Cuprous chloride reacted vigorously to give a reagent-insoluble mixture of cuprous and cupric fluorides; in one experiment 70% of the copper was shown by an iodometric determination to be in the cupric state. Thallous chloride was converted into an insoluble mixture of thallous and thallic fluorides, analysis showing 80—90% of thallium in the product to be in the tervalent state. Lead fluoride, chloride, and bromide gave products containing up to 20% of the tetrafluoride (von Wartenburg, *Z. anorg. Chem.*, 1940, **244**, 337). A similar result was obtained with cobaltous chloride, the product consisting mainly of cobaltic fluoride. Aluminium and ferric chlorides were converted slowly into their respective fluorides; there was no evidence of bromine trifluoride retention. In all these instances the insolubility of the fluorides presumably restricted the conversion, for uranous fluoride was rapidly and quantitatively converted into the hexafluoride (which volatilised as it was formed), and no visible residue remained. Ammonium fluoride and chloride both reacted explosively with bromine trifluoride.

Reactions of Potassium, Silver, and Barium Bromofluorides.—The dissociation pressure of potassium bromofluoride at room temperature is very small, for a 1·1-g. sample kept in a silica flask connected to a vacuum line lost only 0·5% by weight in 6 hours. Decomposition is rapid only above 280°. In contact with glass, the compound is slowly decomposed with the liberation of bromine. Potassium bromofluoride decomposes rapidly with water, but the reaction is not violent like that of bromine trifluoride. Shaken with potassium iodide solution, it liberates iodine immediately, but neither in neutral nor in acid solution does the iodine liberation correspond with the expected 4 equivs. per g.-mol. of the salt; the

values obtained varied from 2·5 to 3·5. Since both fluorine and bromine are recovered quantitatively in the analysis of potassium bromofluoride involving its initial decomposition by water, this loss of oxidising power cannot be due to the formation of fluorine monoxide and must be due to the liberation of oxygen. This has been confirmed qualitatively. Free bromine, as well as oxygen, is formed on treating the bromofluoride with water, and a stable bromine oxyacid which is not reduced by ammonia (bromic acid) remains in solution; it is suggested that these are all decomposition products of bromous acid. The reactions of silver and barium bromofluorides with water were shown to be qualitatively similar to that of the potassium compound.

X-Ray powder photographs of samples of several preparations of potassium bromofluoride sealed in Pyrex tubes were taken, Cu-$K\alpha$ radiation being used. The salt showed slight local decomposition in the *X*-ray beam, but lines due to potassium fluoride were completely absent from the photographs. The method is being applied to the more detailed study of the bromofluorides prepared, as well as to the elucidation of the nature of the more complex products referred to above.

When the potassium compound was heated to *ca.* 280° in a platinum crucible, the metal was strongly attacked with the formation of a brown product. Taking the loss in weight of the crucible as a measure of the platinum used, quantitative figures obtained are consistent with the conversion of platinum into the tetrafluoride and decomposition of the bromofluoride to fluoride; the solid reaction products contained no bromine. 1·507 G. of $KBrF_4$ reacted with 0·579 g. of Pt, equivalent to 0·804 g. of PtF_4. The total weight of solid products was 1·253 g., hence the weight of KF was 1·253 − 0·804 = 0·449 g. The weight, assuming conversion of $KBrF_4$ into KF, should be 0·448 g. The reaction product was left in contact with water for a week, during which time potassium fluoroplatinate crystallised. After recrystallisation from boiling water this was analysed for platinum by heating to constant weight at 1400° (Schlesinger and Tapley, *loc. cit.*) (Found: Pt, 50·4, 49·9. Calc. for K_2PtF_6: Pt, 50·2%). The observations of Schlesinger and Tapley on the impossibility of quantitatively reducing platinum compounds in fluoride-containing solution were extended by an unsuccessful attempt to determine the metal by reduction with magnesium ribbon (Found: Pt 46·8%).

One of the authors is indebted to Imperial Chemical Industries Ltd. (General Chemicals Division) for a maintenance grant.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, January 15th,* 1948.]

---

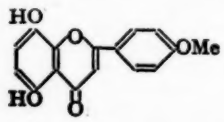
431. *The Structure of Ginkgetin. Part I. Synthesis of 5 : 8-Dihydroxy-4′-methoxyflavone.*

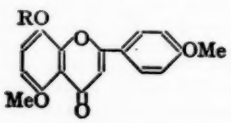
By WILSON BAKER and G. F. FLEMONS.

5 : 8-Dihydroxy-4′-methoxyflavone (I) has been synthesised, and is not identical with ginkgetin, thus confirming the earlier suggestion that the latter is a flavone of more complex nature. The synthesis was achieved *via* 2 : 3-dihydroxy-6-methoxyacetophenone (III), new methods for the preparation of which have been developed.

THE yellow phenolic colouring matter of the autumnal leaves of the maidenhair tree (*Ginkgo biloba*, L.), since termed ginkgetin, was first investigated by Furukawa (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1932, **19**, 27; 1933, **21**, 278) who suggested on somewhat inconclusive evidence that it was probably 5 : 8-dihydroxy-4′-methoxyflavone (I). The synthesis of a number of derivatives of 5 : 8 : 4′-trihydroxyflavone and comparison with the corresponding derivatives of the natural pigment showed, however, that it was most unlikely that ginkgetin could be the simple flavone (I), but was almost certainly a more complex, closely related compound of higher molecular weight (Baker and Simmonds, *J.*, 1940, 1370).

This conclusion has now been confirmed by the synthesis of 5 : 8-*dihydroxy-4′-methoxyflavone* (I) (m. p. 215°, decomp.), which is clearly not identical with ginkgetin (m. p. 238—240°, Furukawa), but nevertheless bears a very close resemblance to it. Both substances give stable, green colorations with alcoholic ferric chloride, and (I) therefore affords an example of a quinol derivative exhibiting a reaction usually regarded as characteristic of a 1 : 2-dihydroxybenzene (other cases are 3 : 6-dihydroxy-2-methoxyacetophenone and primetin, 5 : 8-dihydroxyflavone; see Baker, *J.*, 1939, 956). The investigation of ginkgetin itself is in progress.

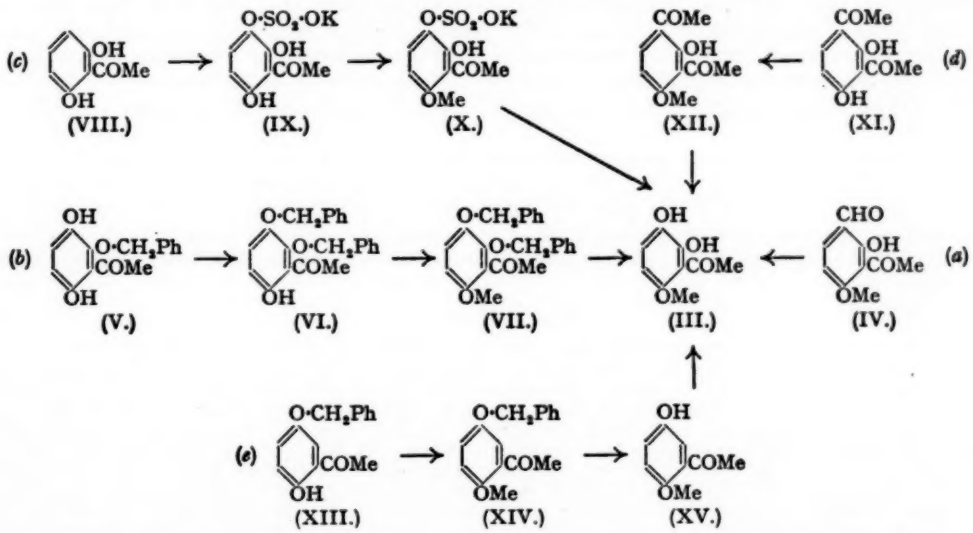
(I.) 



(II.)

The intermediate required for the synthesis of 5 : 8-dihydroxy-4′-methoxyflavone (I) is 2 : 3-dihydroxy-6-methoxyacetophenone (III) which has been prepared by Nakazawa (*J. Pharm. Soc. Japan*, 1939, **59**, 199; see *Chem. Abs.*, 1940, **34**, 1017) by formylation of 2-hydroxy-6-

methoxyacetophenone under the conditions of the Gattermann reaction to give 2-hydroxy-6-methoxy-3-formylacetophenone (IV), and oxidising this with hydrogen peroxide in presence of one equivalent of alkali (process *a*). A considerably improved formylation process is now described, but we find that the aldehyde (IV), whether prepared by Nakazawa's method (zinc cyanide) or by the improved process (hydrogen cyanide), is bright yellow, whereas Nakazawa describes it as colourless, though we agree as to its melting point. In view, however, of the fact that the aldehyde (IV) possesses a nuclear acetyl group, it was thought possible that it might have undergone intermolecular condensation to a chalkone which would undoubtedly be yellow, but this was excluded by the analysis and molecular weight, and by the ready oxidation in good yield to 2 : 3-dihydroxy-6-methoxyacetophenone (III), the structure of which has been established by four further independent synthetical methods (see below). An attempt was made to prepare the chalkone from the aldehydic acetophenone (IV), but the compound was, rather remarkably, recovered unchanged after treatment with alcoholic potassium hydroxide. It was noted, however, that the aldehyde undergoes change on keeping or prolonged drying, the carbon content slowly increases by several units %, the colour tends to deepen, the melting point falls slightly, and the material then shows signs of non-homogeneity and gives a yellow colour with boric and citric acids in acetone, a test which is supposed to be diagnostic for the grouping $-\overset{|}{C}(OH)-\overset{|}{C}-CO-C=\overset{|}{C}-$ (Wilson, *J. Amer. Chem. Soc.*, 1939, **61**, 2303; Wolfram, Mayhan, Morgan, and Johnson, *ibid.*, 1941, **63**, 1248). It may be noted that the position of the formyl group in (IV) is established by the facts that (1) the related dihydroxy-compound (III) prepared from it by the Dakin reaction shows the colour and expected properties of a 2 : 3-dihydroxy-carbonyl compound (see Baker, *J.*, 1934, 1688; Baker and Smith, *J.*, 1936, 346), and (2) the flavone ultimately synthesised is methylated to 5 : 8 : 4'-trimethoxyflavone (II; R = Me) and not the isomeric 5 : 6 : 4'-trimethoxyflavone. An attempt to prepare 2 : 6-dihydroxy-3-formylacetophenone by treating β-resorcylaldehyde with acetonitrile under the conditions of the Hoesch reaction led to the production of dark, intractable material.



The alternative syntheses of 2 : 3-dihydroxy-6-methoxyacetophenone (III) are the following. (*b*) *From* 3 : 6-*dihydroxy-2-benzyloxyacetophenone* (V). The ketone (V) (Baker, Brown, and Scott, *J.*, 1939, 1924) was benzylated to 6-*hydroxy*-2 : 3-*dibenzyloxyacetophenone* (VI), the free hydroxyl group in (VI) methylated with production of 2 : 3-*dibenzyloxy*-6-*methoxyacetophenone* (VII), and the benzyl groups removed by hydrolysis with hydrochloric acid giving (III). (*c*) *From* 2 : 6-*dihydroxyacetophenone* (VIII). Baker, Brown, and Scott (*loc. cit.*) oxidised the acetophenone (VIII) with alkaline potassium persulphate, and hydrolysed the resulting solution of the potassium phenyl sulphate derivative (IX) to 2 : 3 : 6-trihydroxyacetophenone. The intermediate (IX) has now been monomethylated in alkaline solution to (X), and removal of the sulphato-group by acid hydrolysis gave 2 : 3-dihydroxy-6-methoxyacetophenone (III). This method is a general one for the preparation of quinol monoalkyl ethers of known orient-

ation, and is described by Baker and Brown elsewhere (*J.*, in the press). (*d*) *From* 2 : 4-*diacetylresorcinol* (XI). 2 : 4-Diacetylresorcinol (XI) was monomethylated to 2-*hydroxy*-4-*methoxy*-3-*acetylacetophenone* (XII), and (XII) was then oxidised by hydrogen peroxide under the conditions of the Dakin reaction, giving (III). (*e*) *From* 2 : 5-*dihydroxyacetophenone*. Monobenzylation of 2 : 5-dihydroxyacetophenone gave 2-*hydroxy*-5-*benzyloxyacetophenone* (XIII), methylation then yielded 5-*benzyloxy*-2-*methoxyacetophenone* (XIV), and debenzylation then gave 5-*hydroxy*-2-*methoxyacetophenone* (XV). Reactivity in (XV) was expected to be exhibited in position 6 by analogy with the behaviour of its *O*-allyl ether (Baker and Lothian, *J.*, 1936, 276), and oxidation of (XV) by alkaline potassium persulphate gave directly 2 : 3-dihydroxy-6-methoxyacetophenone (III) as the sole isolable product. As with other such persulphate oxidations involving the introduction of a new hydroxyl group into the ortho-position of a phenol, the yield was very poor (see Baker and Brown, *loc. cit.*). Of the five separate methods used for the preparation of (III), probably the most convenient is route (*a*), which has been studied in some detail and involves seven steps from resorcinol, some of which are tedious; route (*d*), requiring five steps from resorcinol, is potentially much simpler but involves the separation of pure 2 : 4-diacetylresorcinol from 4 : 6-diacetylresorcinol, which has not yet been satisfactorily achieved in a simple manner.

Fusion of (III) with anisic anhydride and sodium anisate, and alkaline hydrolysis of the product gave 8-hydroxy-5 : 4′-dimethoxyflavone (II; R = H) in poor yield; most of the material used in this investigation was prepared in this manner. A somewhat improved yield of (II; R = H) may be obtained by isolation of the intermediate 8-*anisoyloxy*-5 : 4′-*dimethoxyflavone* (II; R = anisoyl), and removal of the anisoyl group with aqueous-alcoholic hydrochloric acid. No improvement was effected in the fusion process by substituting 2 : 3-*dianisoyloxy*-6-*methoxyacetophenone* for (III), and only a minute yield of (II; R = H) was obtained by treatment of the same compound with sodamide in benzene to cause molecular rearrangement to the corresponding 1 : 3-diketone, followed by ring closure and hydrolysis (Baker, *J.*, 1933, 1381). Methylation of 8-hydroxy-5 : 4′-dimethoxyflavone (II; R = H) gave 5 : 8 : 4′-trimethoxyflavone (II; R = Me) identical with that previously prepared in another manner by Baker and Simmonds (*J.*, 1940, 1373). Partial demethylation of (II; R = H) with anhydrous aluminium chloride in nitrobenzene gave the desired 5 : 8-dihydroxy-4′-methoxyflavone (I), characterised as its *diacetyl* derivative. The preparation of the flavone (II; R = H) from (III) is unexpectedly difficult; the yields are very small, and the products difficult to obtain pure.

An attempt was made to prepare 6-hydroxy-2-anisoyloxyacetophenone, a possible intermediate in a synthesis of (I). Molecular quantities of 2 : 6-dihydroxyacetophenone and anisoyl chloride in pyridine gave a mixture of 2 : 6-*dianisoyloxyacetophenone* and the monoanisoyl derivative which could not be effectively separated; the latter compound is rapidly hydrolysed by cold N/1-sodium hydroxide solution, and could not be prepared by the Baumann–Schotten technique.

Experimental.

2-*Hydroxy*-6-*methoxy*-3-*formylacetophenone* (2-*Hydroxy*-4-*methoxy*-3-*acetylbenzaldehyde*) (IV).—The formylation in 36% yield of 2-hydroxy-6-methoxyacetophenone by the Gattermann reaction using zinc cyanide has been described by Nakazawa (*loc. cit.*), but we find that the reaction proceeds much more cleanly in 68% yield by the use of anhydrous hydrogen cyanide in presence of aluminium chloride.

To a solution of anhydrous aluminium chloride (3·5 g.) in dry ether (25 c.c.), cooled in an ice–salt bath, was added 2-hydroxy-6-methoxyacetophenone (4·15 g.; Baker, *J.*, 1939, 959), and anhydrous hydrogen cyanide (3·5 c.c.), and hydrogen chloride was passed in for 1½ hours at 0°. After 18 hours at room temperature dry ether was added till no further precipitation occurred, the ether decanted, the residue washed twice with ether, cooled to 0°, and treated with water (25 c.c.). Hydrolysis of the aldimine was effected by heating on the water-bath for 15 minutes, the crude aldehyde extracted with chloroform, and after removal of the solvent the product was ground with silver sand and extracted continuously with light petroleum (b. p. 60—80°) at the b. p. of the solvent for many hours until the extract became colourless. The extracted material was recrystallised from ethyl alcohol, giving pure 2-hydroxy-6-methoxy-3-formylacetophenone as bright yellow needles (3·3 g.), m. p. 89° (Found: C, 62·0; H, 5·3. Calc. for $C_{10}H_{10}O_4$: C, 61·9; H, 5·2%). Nakazawa (*loc. cit.*) describes the compound as colourless prisms, m. p. 89·5°, but we have been quite unable to bring about any loss of colour. It gives a brownish-red coloration with alcoholic ferric chloride.

2 : 3-*Dihydroxy*-6-*methoxyacetophenone* (III).—(a) *From* 2-*hydroxy*-6-*methoxy*-3-*formylacetophenone* (IV). The oxidation of (IV) by the Dakin reaction was effected in 65% yield in N/1-sodium hydroxide (1 mol.) with 3% hydrogen peroxide (1·1 mols.) after the manner described by Nakazawa (*loc. cit.*). The oxidation cannot be successfully carried out if, as is usual, more than 1 equiv. of alkali is used; this modification of the Dakin reaction may find other applications where the normal procedure fails. 2 : 3-Dihydroxy-6-methoxyacetophenone forms bright yellow needles from aqueous acetone, m. p. 147—148° (Found: C, 59·2; H, 5·5. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%). It gives a very strong

green ferric chloride reaction in alcoholic solution, but unlike other 2 : 3-dihydroxyacetophenones it gives no precipitate in dilute alcoholic solution with neutral lead acetate.

(b) *From* 2 : 3-*dibenzyloxy*-6-*methoxyacetophenone* (VII) (see below). Debenzylation of (VII) (0·1 g.) was effected by heating in glacial acetic acid (2 c.c.) and concentrated hydrochloric acid (1 c.c.) for 1 hour at 60°. The product, isolated by dilution and extraction with ether, was crystallised from ethyl acetate at a low temperature, giving a yellow, microcrystalline product, m. p. 145—146°, showing no depression of m. p. when mixed with 2 : 3-dihydroxy-6-methoxyacetophenone, m. p. 146—147°, prepared by method (a).

(c) *From* 2 : 6-*dihydroxyacetophenone* (VIII) via (IX) *and* (X). 2 : 6-Dihydroxyacetophenone (9 g.; 1 mol.) in a solution of sodium hydroxide (12 g.; 5 mols.) in water (110 c.c.) was stirred at room temperature for 4 hours during the addition of a solution of potassium persulphate (17·5 g.; 1·1 mols.) in water (400 c.c.). The green solution, after standing overnight, was acidified to Congo-red, filtered from red, flocculent material (charcoal), extracted twice with ether, made alkaline to litmus, and evaporated to a small bulk (50 c.c.) at 50—60° under diminished pressure. After addition of acetone (10 c.c.) the intermediate sulphato-compound was methylated by vigorous shaking for 1½ hours with portionwise addition of potassium hydroxide (5 g.) in water (5 c.c.) and methyl sulphate (7·5 g.). After standing overnight and addition of water to dissolve the precipitated salts, the solution was acidified to Congo-red and extracted with ether, concentrated hydrochloric acid (50 c.c.) was added, and the mixture was heated on the steam-bath for ½ hour under a layer of light petroleum (b. p. 60—80°; 250 c.c.). The hydrolysis and extraction were repeated, and the extracts united and distilled, leaving a yellow solid (0·4 g.) which was crystallised from dilute methyl alcohol (charcoal), and then from a small volume of benzene, being obtained in brownish-yellow prisms, m. p. and mixed m. p. 148—149°.

(d) *From* 2-*hydroxy*-6-*methoxy*-3-*acetylacetophenone* (XII) (see below). To (XII) (0·52 g.; 1 mol.) dissolved in N/1-sodium hydroxide (5 c.c.; 2 mols.) was added 3% hydrogen peroxide (6·6 c.c.; 1·15 mols.). The temperature rapidly rose from 22° to 47° and the solution darkened. After 2 hours' standing, addition of acid precipitated 2 : 3-dihydroxy-6-methoxyacetophenone (III) (0·15 g.; 33% yield), m. p. 145—146·5°. One recrystallisation from 50% aqueous acetone gave bright yellow needles, m. p. and mixed m. p. 147—148°.

(e) *From* 5-*hydroxy*-2-*methoxyacetophenone* (XV) (see below). (With Mr. F. Glockling.) A solution of 5-hydroxy-2-methoxyacetophenone (3 g.; 1 mol.) in water (60 c.c.) containing sodium hydroxide (5 g.) was stirred for 5 hours during the addition of a solution of potassium persulphate (4·6 g.; 0·95 mol.) in water (150 c.c.). After 48 hours the mixture was made just acid to Congo-red, extracted with ether, rendered more strongly acid, and refluxed for 1 hour under a layer of ether (100 c.c.) The ether layer was separated, and the process repeated. The united extracts left a brown oil which yielded to hot benzene well-crystalline 2 : 3-dihydroxy-6-methoxyacetophenone (III) (40 mg.). From dilute acetone it formed yellow needles, m. p. and mixed m. p. 146—148°.

6-*Hydroxy*-2 : 3-*dibenzyloxyacetophenone* (VI) *and* 2 : 3 : 6-*Tribenzyloxyacetophenone.*—3 : 6-Dihydroxy-2-benzyloxyacetophenone (V) (12·9 g.; 1 mol.; Baker, Brown, and Scott, *loc. cit.*), anhydrous acetone (40 c.c.), anhydrous potassium carbonate (15 g.), and benzyl chloride (7 g.; 1·1 mols.) were stirred and refluxed for 10 hours, with the addition of more potassium carbonate (10 g.) after 3 hours. The dark product was treated with water (750 c.c.) and 5% sodium hydroxide (100 c.c.), extracted 4 times with ether, leaving some undissolved tarry material, and the ethereal extracts yielded a deep brown syrup which partially crystallised and was pressed on a porous tile. The resulting solid 2 : 3 : 6-*tribenzyloxyacetophenone*, after several crystallisations from alcohol (charcoal), formed almost colourless prisms (0·7 g.), m. p. 110° (Found : C, 79·4; H, 6·1. $C_{29}H_{26}O_4$ requires C, 79·4; H, 5·9%).

The yellow alcoholic mother-liquors from the crystallisation of the 2 : 3 : 6-tribenzyloxyacetophenone after some concentration and cooling in ice deposited crystals which, after recrystallisation from alcohol, formed short, canary-yellow prisms (1·65 g.), m. p. 57·5° (Found : C, 75·8; H, 5·7. $C_{22}H_{20}O_4$ requires C, 75·8; H, 5·7%). This 6-*hydroxy*-2 : 3-*dibenzyloxyacetophenone* (VI) is quite insoluble in cold aqueous alkalis, but gives an intense green coloration with alcoholic ferric chloride.

2 : 3-*Dibenzyloxy*-6-*methoxyacetophenone* (VII).—The hydroxy-compound (VI) was treated under vigorous conditions in acetone with a large excess of 20% aqueous potassium hydroxide and methyl sulphate. After dilution with water the precipitated oil was extracted with ether and distilled, giving the *methoxy*-compound as a yellow, very viscous oil, b. p. *ca.* 220—224° (oil-bath temp.)/0·1 mm. (Found : C, 76·2; H, 6·3. $C_{23}H_{22}O_4$ requires C, 76·2; H, 6·1%).

2 : 4-*Diacetylresorcinol* (XI).—Resacetophenone (Robinson and Shah, *J.*, 1934, 1494) is most conveniently monoacetylated (95% yield) by an application of the technique due to Simokoriyama (*Bull. Chem. Soc. Japan*, 1941, **46**, 284). Resacetophenone (97 g.; 1 mol.) was stirred for ½ hour with acetic anhydride (330 g.; 5 mols.) and pyridine (3 c.c.), warmed to 45°, cooled, and poured into water (1 l.), yielding 4-*O*-acetylresacetophenone (118 g.), m. p. 75—76°. From this compound (100 g.), a mixture (90 g.; m. p. 77—148°) of 2 : 4-diacetylresorcinol (XI) and 4 : 6-diacetylresorcinol was prepared according to Baker (*J.*, 1934, 1690). The 2 : 4-diacetylresorcinol was finally obtained in a purer state than previously recorded by repeated crystallisation from methyl alcohol, and then formed fine, very pale yellow needles, m. p. 92° (lit. m. p. 89°) (Found : C, 61·8; H, 5·2. Calc. for $C_{10}H_{10}O_4$: C, 61·8; H, 5·2%).

2-*Hydroxy*-6-*methoxy*-3-*acetylacetophenone* (XII).—Pure 2 : 4-diacetylresorcinol (XI) (m. p. 92°; 1·21 g.; 1 mol.) was refluxed with dry acetone (15 c.c.), anhydrous potassium carbonate (2·2 g.; 2·5 mols.) and methyl sulphate (0·65 c.c.; 1·1 mols.) for 8 hours, then diluted, boiled, and acidified. The precipitated 2-*hydroxy*-6-*methoxy*-3-*acetylacetophenone* was crystallised twice from alcohol and obtained as stout, colourless prisms (0·65 g.), m. p. 104° (Found : C, 63·7; H, 5·7. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%). The compound gives a brownish-red coloration with alcoholic ferric chloride.

2-*Hydroxy*-5-*benzyloxyacetophenone* (XIII). (With Mr. F. Glockling.)—2 : 5-Dihydroxyacetophenone (120 g.; m. p. 198—200°) was stirred and refluxed for 10 hours with acetone (600 c.c.), anhydrous potassium carbonate (250 g.), and benzyl chloride (110 g.). The filtered liquor was treated with charcoal, the acetone distilled off, the residue dissolved in ether, and the ethereal solution shaken

with aqueous sodium hydroxide, dried, and distilled finally under diminished pressure to remove unchanged benzyl chloride. The residual 2-*hydroxy*-5-*benzyloxyacetophenone*, after crystallisation from methyl alcohol, formed yellow needles (60 g.), m. p. 69—70° (Found: C, 73·9; H, 5·5. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%). It is insoluble in aqueous sodium hydroxide, but gives a dull slate-blue colour with alcoholic ferric chloride.

5-*Benzyloxy*-2-*methoxyacetophenone* (XIV). (With Mr. F. GLOCKLING.)—The preceding compound (XIII) (50 g.) was vigorously shaken in acetone (200 c.c.) with methyl sulphate (80 c.c.) and a solution of potassium hydroxide (150 g.) in water (500 c.c.) for 10 minutes, refluxed for ½ hour, and the acetone layer separated. The aqueous layer was extracted with ether, the extract added to the acetone layer, distilled, and the residual solid mass crystallised from methyl alcohol, giving colourless needles (54 g.). For analysis the 5-*benzyloxy*-2-*methoxyacetophenone* was crystallised from ethyl alcohol and then from light petroleum (b. p. 40—60°); needles, m. p. 56° (Found: C, 74·8; H, 6·1. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%).

5-*Hydroxy*-2-*methoxyacetophenone* (XV). (With Mr. F. GLOCKLING.)—Compound (XIV) (52 g.) was treated for 1 hour at 65—70° with acetic acid (300 c.c.) and concentrated hydrochloric acid (120 c.c.), poured into water (1 l.), and extracted with ether. The ethereal solution was extracted into aqueous sodium hydroxide, and the alkaline layer separated, acidified, and extracted with ether. The extract yielded a dark oil which was crystallised first from chloroform (charcoal) and then from water, yielding finally 5-*hydroxy*-2-*methoxyacetophenone* (10·3 g.) as faintly yellow needles, m. p. 83° after drying in a vacuum at 65° (Found: C, 65·3; H, 6·0. $C_9H_{10}O_3$ requires C, 65·0; H, 6·0%). It gives no characteristic coloration with alcoholic ferric chloride.

8-*Hydroxy*-5:4′-*dimethoxyflavone* (II; R = H).—2:3-Dihydroxy-6-methoxyacetophenone (4 g.), anisic anhydride (28 g.), and sodium anisate (4 g.) were stirred at 180—190° for 7 hours. The product was now dissolved in a mixture of alcohol (200 c.c.) and a little water, refluxed for ¼ hour with an excess of 30% aqueous potassium hydroxide, most of the alcohol removed by distillation, and the cold diluted solution saturated with carbon dioxide. The dark brown amorphous solid was crystallised first from alcohol (600 c.c.) (charcoal), and then twice from glacial acetic acid (40 c.c.), being obtained as thin, honey-yellow prisms (0·4 g.), m. p. 267° (Found, in material heated for several hours at 145° in a vacuum over potassium hydroxide: C, 67·9; H, 4·6; MeO, 19·3. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7; MeO, 20·8%). This 8-*hydroxy*-5:4′-*dimethoxyflavone* tenaciously retains a trace of acetic acid, which can only be completely expelled by fusion.

Acetylation by means of acetic anhydride at the b. p. for 5 hours, concentration and addition of water, and crystallisation from alcohol gave a mixture of pale yellow prisms (A), and clusters of fine, colourless needles (B). Product (A) (m. p. 171°) is assumed to be 8-*acetoxy*-5:4′-*dimethoxyflavone*; recrystallisation from alcohol gave colourless needles, m. p. 172° (Found: C, 66·8; H, 5·0. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·7%). Product (B), unlike recrystallised (A), becomes yellow on drying at room temperature, but it has not been further investigated.

8-*Anisoyloxy*-5:4′-*dimethoxyflavone* (II; R = anisoyl).—The fusion product obtained as described in the preceding section was treated with a hot mixture of ethyl acetate (200 c.c.) and water (50 c.c.), cooled, shaken for ¼ hour with 10% aqueous sodium carbonate (150 c.c.), and the whole filtered.* The residual solid was washed successively with aqueous sodium carbonate, water, and ethyl acetate, dried (2·3 g.), and crystallised from ethyl acetate (600 c.c.), giving light brown prisms, m. p. 225° (1·48 g.), and a further crop (0·46 g.) was obtained from the mother-liquor. Recrystallisation from alcohol gave 8-*anisoyloxy*-5:4′-*dimethoxyflavone* as long, lustrous, cream-coloured needles, which, after drying at 145° in a vacuum over phosphoric anhydride, had m. p. 225·5° [Found: C, 69·2; H, 4·7; OMe, 18·4; *M* (Rast), 399. $C_{25}H_{20}O_7$ requires C, 69·4; H, 4·7; OMe, 21·5%; *M*, 432]. Hydrolysis to 8-hydroxy-5:4′-dimethoxyflavone (II; R = H) was brought about in 72% yield by refluxing for 12 hours with a large volume of alcohol containing one-third of its volume of concentrated hydrochloric acid, the mixture being finally distilled with the addition of water till no further separation of crystals occurred. The product, after crystallisation from a very large volume of alcohol, had m. p. 267°, undepressed on admixture with the specimen previously described.

From the ethyl acetate layer above * were obtained by repeated concentration and crystallisation (*a*) 0·36 g. of 8-anisoyloxy-5:4′-dimethoxyflavone, m. p. 224·5°, and (*b*) a more soluble compound (0·45 g.) separating from alcohol in fine, pale cream-coloured needles, m. p. 224·5—225°, and at 197—204° when mixed with 8-anisoyloxy-5:4′-dimethoxyflavone (Found: C, 70·0; H, 4·9; OMe, 22·0. $C_{33}H_{26}O_9$ requires C, 69·9; H, 4·6; OMe, 21·9%). There can be little doubt that this compound is 8-*anisoyloxy*-5:4′-*dimethoxy*-3-*anisoylflavone*.

2:3-*Dianisoyloxy*-6-*methoxyacetophenone*.—To a solution of 2:3-dihydroxy-6-methoxyacetophenone (3·64 g.; 1 mol.) in anhydrous pyridine (25 c.c.) was added anisoyl chloride (8·6 g.; 2·5 mols.) with stirring, and the mixture heated on the water-bath for ½ hour. Cautious addition of dilute hydrochloric acid yielded 2:3-*dianisoyloxy*-6-*methoxyacetophenone* as a solid which separated from alcohol (400 c.c.) in very pale cream-coloured prisms (7·75 g.; 86%); after a further recrystallisation it had m. p. 164·5° (Found: C, 66·6; H, 4·9. $C_{25}H_{22}O_8$ requires C, 66·7; H, 4·9%).

5:8:4′-*Trimethoxyflavone*.—8-Hydroxy-5:4′-dimethoxyflavone was readily methylated by treatment with methyl sulphate in aqueous potassium hydroxide. The alkali-insoluble product after crystallisation from benzene (charcoal) gave almost colourless prisms, m. p. 162·5° (Found, in material dried at 80° in a vacuum: C, 69·4; H, 5·5. Calc. for $C_{18}H_{16}O_5$: C, 69·2; H, 5·2%). A specimen of 5:8:4′-trimethoxyflavone, m. p. 161°, prepared by the method of Baker and Simmonds (*loc. cit.*), after crystallisation from alcohol (charcoal) and then benzene had m. p. 162·5°, either alone or when mixed with the flavone prepared as above.

5:8-*Dihydroxy*-4′-*methoxyflavone* (I).—8-Hydroxy-5:4′-dimethoxyflavone (II; R = H) (0·32 g.), anhydrous aluminium chloride (0·2 g.), and freshly distilled nitrobenzene (6 c.c.) were heated at 100° for 1 hour. To the dark product was added dilute hydrochloric acid, the nitrobenzene removed in steam, and the yellow-brown solid collected, washed, and dried. It was crystallised from dilute acetic acid (300 c.c.), giving bright yellow prisms, m. p. 215° (decomp.). This flavone tenaciously retained a

trace of acetic acid from which it could not be entirely freed (Found, in material dried at 145° in a vacuum over potassium hydroxide for 2 hours: C, 64·3; H, 4·1; for 4 hours: C, 65·7; H, 4·3; for 36 hours: C, 66·1; H, 4·1; OMe, 10·4. $C_{15}H_9O_4$·OMe requires C, 67·6; H, 4·2; OMe, 10·9%). 5:8-*Dihydroxy-4'-methoxyflavone* gives a strong green coloration with alcoholic ferric chloride, and dissolves in aqueous sodium hydroxide with an orange colour. It does not give a red colour when reduced with magnesium and hydrochloric acid, as does ginkgetin.

The *diacetyl* derivative, prepared in the usual way, was twice crystallised from alcohol (charcoal) and then from benzene, forming aggregates of minute needles, m. p. 230° [Found: C, 64·8; H, 4·4; Ac, 28·2. $C_{16}H_{10}O_3(OAc)_2$ requires C, 65·2; H, 4·3; Ac, 23·3%]. The diacetyl derivative of ginkgetin has m. p. 226—228° (Furukawa).

2:6-*Dianisoyloxyacetophenone*.—2:6-Dihydroxyacetophenone (10 g.) in anhydrous pyridine (40 c.c.) was slowly treated, whilst being shaken and cooled, with anisoyl chloride (11·2 g.; 1 mol.), and finally heated on the water-bath for 20 minutes, cooled, and dilute hydrochloric acid added. The product (19 g.) which solidified was ground, washed with water, and crystallised several times from alcohol (100 c.c.), giving a powder, melting at 99—99·5° to a turbid liquid which cleared at 105°. No effective method was found of isolating both constituents of this mixture in the pure state, but the higher-melting product, 2:6-*dianisoyloxyacetophenone*, was obtained by crystallisation from benzene–light petroleum and then from alcohol, in fine, colourless prisms, m. p. 141° (Found: C, 68·6; H, 4·9. $C_{24}H_{20}O_7$ requires C, 68·6; H, 4·8%).

The authors' thanks are due to Imperial Chemical Industries Ltd. and to the Colston Research Society for grants which have defrayed part of the cost of this research, and to Mr. F. Glockling for preparing a quantity of 2:6-dihydroxyacetophenone.

THE UNIVERSITY, BRISTOL. [*Received, January 26th*, 1948.]

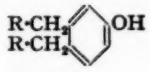
---

432. *Substitution in 3:4-Dialkylphenols.*

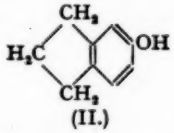
By G. D. PARKES.

The coupling of diazonium salts and some 3:4-dialkylphenols has been investigated and the proportions in which reaction takes place, in the 2- and 6-positions respectively, have been determined. The results seem to show that the variation in activation energies for reaction as either one of the Kekulé structures, shown by Sutton and Pauling to be theoretically possible as the result of valency deflexion brought about by fusion of saturated rings on to a benzene ring, can also occur as a consequence of steric hindrance between groups in the ortho-position to each other.

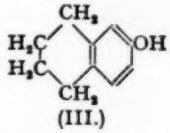
THE proportions in which coupling between solutions of diazonium salts and *as-o*-xylenol (3:4-diethylphenol) takes place in the 2- and 6-positions respectively was investigated by Diepolder (*Ber.*, 1909, **42**, 2916) who found that coupling occurred to the extent of 83% in the 6-position and 17% in the 2-position. Mills and Nixon (*J.*, 1930, 2510) investigated the coupling of diazonium salts with 5-hydroxyindane (which reacted almost entirely in the 6-position) and with tetrahydro-β-naphthol where reaction was almost exclusively in the 1-position. These results were interpreted by Mills and Nixon as indicating a high degree of " fixation " of the double bonds of the Kekulé formula for benzene; that in a 1:2-dialkyl-4-phenol the more stable arrangement of bonds is that represented by (I) and that in the light of Diepolder's results



(I.)



(II.)



(III.)

the arrangement of the bond system postulated for 5-hydroxyindane (II) is the normal arrangement whereas that in tetrahydro-β-naphthol (III) is an abnormal arrangement brought about through the attachment to the benzene nucleus of the tetramethylene chain.

The last statement seemed, at first, to contradict some of the other stereochemical considerations brought forward by Mills and Nixon and it was thought more probable that as the alkyl groups in the dialkylphenol became larger the steric effects of these groups on each other would tend to change the stable arrangements of the bonds from one form to the other. Later work (compare Fieser and Lothrop, *J. Amer. Chem. Soc.*, 1936, **58**, 2050; 1937, **59**, 945; Sidgwick and Springall, *J.*, 1936, 1532; Placzek, *Leipziger Vorträge*, 1931, 71; Ingold, *et al.*, *J.*, 1936, 966) and, in particular, the development of the theory of resonance, has made it impossible to uphold the idea that benzene can, under any conditions, be represented by one single Kekulé

structure. Nevertheless, these results are interesting as indicating the existence of a type of directed reactivity in the benzene ring not previously contemplated.

Sutton and Pauling (*Trans. Faraday Soc.*, 1935, **31**, 939) examined the problem from the point of view of wave mechanics and concluded that the effect of saturated side rings upon the ratio of the coefficients of the wave functions of the two Kekulé structures is relatively small (about 6%) and that the benzene ring retains the greater part of its stabilising resonance energy. Nevertheless, making the reasonable assumption that the ratio of the activation energies, for reaction as either one of the Kekulé structures, depends upon the square of the ratio of the coefficients, it is possible to account for the experimental facts described by Mills and Nixon. (Compare also Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1946, **42**, 756).

Since, therefore, the distortion of the ortho-valencies of benzene, by 5-atom or 6-atom saturated rings fused on to the nucleus, can bring about the variation in the ratio of the activation energies described, it was thought of interest to investigate the possibility of a similar distortion being caused by the steric hindrance of two ortho-substituents not forming part of a ring. The reactivity of 3 : 4-dialkylphenols towards diazotised amines furnishes one method for testing this point since, if the above conclusions are sound, diazotised amines would be expected to show an increasing tendency to couple at position 2 as compared with position 6 as the sizes of the alkyl groups increased.

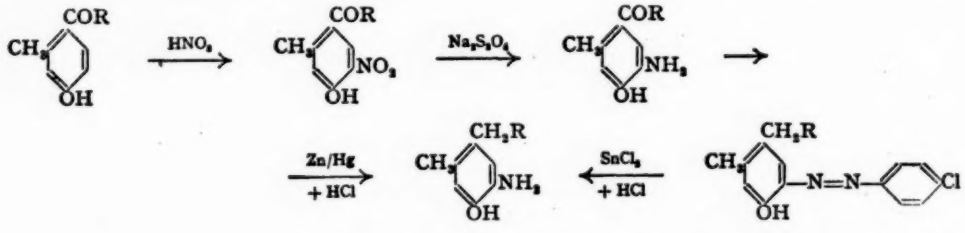
3-Methyl-4-ethylphenol was obtained from 4-acetyl-3-methylphenol (compare Skraup and Poller, *Ber.*, 1924, **57**, 2033) by Clemmensen reduction. 3-Methyl-4-propylphenol was obtained similarly from 4-propionyl-3-methylphenol. The preparation of 3-methyl-4-*iso*propyl- and 3-methyl-4-*iso*butyl-phenol was attempted similarly, as also of 4-methyl-3-ethylphenol, by several methods, but without success.

3 : 4-Diethylphenol was obtained by way of a Grignard reaction with *m*-methoxybenzaldehyde and methyl iodide, the resulting secondary alcohol being esterified with hydrogen chloride and reduced with hydrogen in presence of palladium forming, by removal of the ether-methyl group, *m*-ethylphenol. This was then treated with acetyl chloride in the presence of zinc chloride and the 4-acetyl-3-ethylphenol, so formed, reduced by Clemmensen's method. This method was used since a Friedel–Crafts reaction with acetyl chloride and *m*-methoxyethylbenzene resulted in the formation of the 6-acetyl instead of the desired 4-acetyl compound.

For the coupling reactions *p*-chlorobenzenediazonium chloride was used as it was found that some of the benzeneazo-compounds of the higher phenols are too low melting for easy separation by recrystallisation. Diepolder's experiments were repeated, using benzenediazonium chloride as well as the *p*-chloro-compound, for comparison.

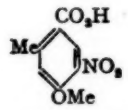
The isomers were separated by fractional crystallisation and the proportions in which each occurred determined. The result was also checked in further experiments by comparing the melting point of the washed and dried " crude " product with the melting-point curve of mixtures of the pure components.

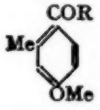
Diepolder (*loc. cit.*) established the orientation of his higher-melting isomer by reducing it to an amino-phenol identical with that obtained from a mononitroxylenol, which he converted into a known nitro-*o*-xylene. This method could not be applied to the present work since nitration of the dialkylphenols concerned gave a mixture of liquid products. The problem was solved by nitrating 4-acetyl-3-methylphenol and 4-propionyl-3-methylphenol, establishing the constitution of the nitro-compounds and then reducing them in stages to the aminomethylalkylphenols and comparing them with the products obtained by fission of the azo-compounds :



The constitution of the mononitro-compounds was established by heating their methyl ethers for a long time with excess of dilute neutral potassium permanganate solution. This gave the same toluic acid (hitherto of uncertain constitution) as was obtained from 5-nitro-*o*-4-xylenol by Cain and Simonsen (*J.*, 1914, 162). This acid must have the structure (IV), since a

toluic acid obtained from (V) must have the methyl and methoxyl groups in the meta-position to one another.

(IV.) 



(V.)

The results of these experiments are shown in the following table:

Phenol.	Percentage of coupling in 2-position.	Percentage of coupling in 6-position.
3 : 4-Dimethylphenol	20	80
3-Methyl-4-ethylphenol	33	67
3-Methyl-4-*n*-propylphenol	55	45
3 : 4-Diethylphenol	45	55

These results seem to show that steric hindrance between the groups in the ortho-position does take place and results in the same kind of variation in the ratio of the activation energies for reaction as one or other of the Kekulé structures as is brought about by the fusion of saturated rings of different sizes on to the benzene nucleus.

Experimental.

Phenols and Derivatives.—4-Acetyl-3-methylphenol (10 g.) (Skraup and Poller, *loc. cit.*) was mixed with hydrochloric acid (200 c.c.) (1 vol. of acid; 2 vols. of water) and amalgamated zinc [made by standing zinc (40 g.) in saturated mercuric chloride (100 c.c.) for 10 minutes], heated under reflux until reaction started, and finally refluxed for several hours. The colourless oil obtained by steam distillation was extracted with ether and dried (Na_2SO_4), the solvent removed, and the product distilled. The 3-methyl-4-ethylphenol, a colourless oil, b. p. 235°, set to a white crystalline solid on scratching in a freezing mixture. Yield, 4 g.

4-Propionyl-3-methylphenol (22 g.), obtained similarly (but compare v. Auwers, *Annalen*, 1924, **439**, 174), was converted into 3-methyl-4-*n*-propylphenol (88 g. of amalgamated zinc; 125 c.c. of conc. hydrochloric acid; 250 c.c. of water). It was a colourless oil, b. p. 252°/759 mm. Yield, 10 g. *3-Methyl-4-n-propylphenoxyacetic acid*, obtained from 2 g. of the phenol, 1 g. of potassium hydroxide in 15 c.c. of water, and 2 g. of chloroacetic acid in 10 c.c. of water, crystallised as small flat rectangular prisms, m. p. 121°, from benzene (Found: C, 69·35; H, 7·66. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·69%).

m-Methoxyphenylmethylcarbinol was prepared by the method described by Klages and Allendorf (*Ber.*, 1898, **31**, 1003), using 133 g. of *m*-methoxybenzaldehyde and 144 g. of methyl iodide. Yield, 110 g. of a colourless viscous oil, b. p. 110°/10 mm. This was converted by the method used by Klages (*Ber.*, 1903, **36**, 3584) for the ortho-compound into 1-chloro-1-*m*-methoxyphenylethane (50 g. from 55 g. of carbinol). The following were prepared similarly: *m*-methoxyphenylethylcarbinol, a colourless viscous oil, b. p. 130°/8 mm., *phenylurethane*, colourless needles, m. p. 47° (Found: N, 5·27. $C_{17}H_{19}O_3N$ requires N, 5·20%); 1-chloro-1-*m*-methoxyphenylpropane, a colourless oil.

m-Methoxyethylbenzene was obtained by reduction of 1-chloro-1-*m*-methoxyphenylethane (40 g.) in methyl alcohol (200 c.c.) by hydrogen in presence of 2% palladium on strontium carbonate and calcium carbonate (45 g.). After filtration of the solution, methyl alcohol was removed by evaporation, and the crude product separated from calcium chloride by adding ether and filtering, evaporating, and distilling the ether solution under reduced pressure. The product was a colourless, mobile liquid, b. p. 74°/10 mm. Yield, 18·5 g. *m*-Methoxypropylbenzene was prepared similarly as a colourless mobile liquid, b. p. 92°/11 mm. Yield, 17·5 g. (Found: C, 80·12; H, 9·29. $C_{10}H_{14}O$ requires C, 80·0; H, 9·3%).

m-Methoxyethylbenzene (10 g.) was demethylated by boiling for 8 hours with acetic acid (15 c.c.) and hydriodic acid (10 g.). Iodine was removed by means of sodium hydrogen sulphite and the *m*-ethylphenol extracted with ether, dried (Na_2SO_4), and distilled under reduced pressure. It was a colourless oil, b. p. 95°/10 mm. Yield, 7 g.

Acetyl chloride (18 g.) was added, dropwise, to *m*-ethylphenol (15 g.) and finely powdered zinc chloride (18 g.) and the mixture kept for 3 days. The solid which separated was filtered off and reduced to 3 : 4-diethylphenol, without further purification, by Clemmensen's method [using 80 g. of zinc, 200 c.c. of concentrated mercuric chloride solution, and 400 c.c. of hydrochloric acid (1 vol. of conc. HCl: 2 vols. of water)], extracted with ether, dried (Na_2SO_4), and distilled under reduced pressure. It was a colourless oil, b. p. 125°/10 mm. Yield, 2 g.

Coupling Reactions.—Diepolder's experiment (*loc. cit.*) was repeated using *as-o*-xylenol and *p*-chlorobenzenediazonium chloride for comparison purposes. Coupling was effected with 3-methyl-4-ethylphenol, 3-methyl-4-propylphenol, and 3 : 4-diethylphenol, using 2 g. of phenol in 30 c.c. of 5% sodium hydroxide and 1·7 g. of *p*-chloroaniline in a mixture of sulphuric acid (2 g.) and water (30 c.c.), diazotized with sodium nitrite (1·2 g.) in water (10 c.c.). The products were filtered off, washed with distilled water, and dried in a vacuum desiccator.

Separation of the Isomers.—When dry, the melting point of the mixture of azo-compounds obtained as above was determined and the mixture was then dissolved in the smallest quantity of alcohol warmed to 30—40°. The solution was allowed to cool slowly to 0°. The crystals which separated were filtered off and recrystallised again from warm alcohol. This process was repeated and the melting point determined after each recrystallisation until the melting point had reached a maximum.

The mother liquor from the first crystallisation was diluted with water (double the volume of alcohol used) and the precipitate filtered off. The subsequent mother liquors from the recrystallisation of the

less soluble isomer were treated similarly and all the precipitates combined, dissolved in just enough alcohol, warmed to 20° and the solution allowed to cool to room temperature. Some of the less soluble isomer separated and was discarded. The more soluble substance was precipitated with water and the melting point taken. The process was repeated until the melting point reached a maximum. Melting-point curves were then compiled for known mixtures of each pair of isomers and from them the composition of the initial mixtures of isomers was deduced.

The following substances were isolated: 6-(p-*chlorobenzeneazo*)-3 : 4-*dimethylphenol*, m. p. 156°, (Found: Cl, 13·6. $C_{14}H_{13}ON_2Cl$ requires Cl, 13·6%); 2-(p-*chlorobenzeneazo*)-3 : 4-*dimethylphenol*, m. p. 109° (Found: Cl, 13·6%); 6-*benzeneazo*-3-*methyl*-4-*ethylphenol*, bright red needles, m. p. 69° (Found: N, 11·6. $C_{15}H_{16}ON_2$ requires N, 11·7%); 2-*benzeneazo*-3-*methyl*-4-*ethylphenol*, light brown microcrystalline powder, m. p. 41° (Found: N, 11·5%); 6-(p-*chlorobenzeneazo*)-3-*methyl*-4-*ethylphenol*, golden brown prisms, m. p. 122° (Found: Cl, 13·0. $C_{15}H_{15}ON_2Cl$ requires Cl, 13·0%); 2-(p-*chlorobenzeneazo*)-3-*methyl*-4-*ethylphenol*, dark brown prisms, m. p. 73·4° (Found: Cl, 13·0%); 6-(p-*chlorobenzeneazo*)-3-*methyl*-4-n-*propylphenol*, brick-red powder, m. p. 115° (Found: Cl, 12·4. $C_{16}H_{17}ON_2Cl$ requires Cl, 12·3%); 2-(p-*chlorobenzeneazo*)-3-*methyl*-4-n-*propylphenol*, orange-red powder, m. p. 90° (Found: Cl, 12·4%); 6-(p-*chlorobenzeneazo*)-3 : 4-*diethylphenol*, m. p. 130° (Found: Cl, 12·2. $C_{16}H_{17}ON_2Cl$ requires Cl, 12·3%); 2-(p-*chlorobenzeneazo*)-3 : 4-*diethylphenol*, m. p. 95° (Found: Cl, 12·4%).

Orientation of the Azo-compounds.—The azo-compound (1 g.) was dissolved in the least quantity of boiling alcohol, and modified Witt's solution (Mills and Nixon, *loc. cit.*) added until the colour was discharged. The solution was diluted to about 400 c.c. with water, saturated when hot with hydrogen sulphide, boiled, filtered immediately, evaporated to small bulk (water-bath), made alkaline with sodium hydroxide, and the *p*-chloroaniline distilled off in steam. The residue was filtered, acidified with dilute acetic acid, and the precipitate filtered off, washed with water, dried, and recrystallised. The 6-*p*-chlorobenzeneazo-3 : 4-dimethylphenol, m. p. 156°, gave 6-amino-3 : 4-dimethylphenol, m. p. 174—175° (decomp.), identical with an authentic specimen prepared by reduction of 6-nitro-3 : 4-dimethylphenol with sodium hydrogen sulphide (compare, Diepolder, *loc. cit.*). The benzeneazo-3-methyl-4-ethylphenol, m. p. 69°, when treated similarly gave 6-amino-3-methyl-4-ethylphenol, m. p. 160° (decomp.), identical with an authentic specimen prepared as described below. The *p*-chlorobenzeneazo-3-methyl-4-ethylphenol, m. p. 122°, gave the same product. The *p*-chlorobenzeneazo-3-methyl-4-*n*-propylphenol, m. p. 115°, gave 6-amino-3-methyl-4-*n*-propylphenol, m. p. 145°, identical with an authentic specimen prepared as described below. The *p*-chlorobenzeneazo-3 : 4-diethylphenol, m. p. 130°, gave 6-amino-3 : 4-diethylphenol, m. p. 146°.

Synthesis of the Necessary Reference Substances.—Nitration of 4-*acetyl*-3-*methylphenol.* The phenol (7 g.) was suspended in 45 c.c. of glacial acetic acid and 2·5 c.c. of concentrated nitric acid (*d* 1·42) in 2·5 c.c. of glacial acetic acid were added slowly with cooling and shaking. The mixture, warmed on a water-bath, became hot and deep red. It was poured on ice, the precipitate of *nitro*-4-*acetyl*-3-*methylphenol* washed, dried, and recrystallised; it formed long, slender, pale brownish-yellow prisms from alcohol, m. p. 129° (Found: N, 7·34. $C_9H_9O_4N$ requires N, 7·2%).

Nitro-4-acetyl-3-methylphenol (3 g.) was added with strirring to sodium hydroxide (0·7 g.) in a little water and heated (water-bath). The bright orange sodium salt was powdered and heated with toluene (1 c.c.) and methyl sulphate (3 c.c.) in an oil-bath (110—120°; 30 minutes). The colourless liquid, diluted with water, was boiled, made alkaline, and cooled. The *methyl ether* formed very pale yellow needles from alcohol, m. p. 98·5° (Found: N, 6·8. $C_{10}H_{11}O_4N$ requires N, 6·7%).

5-*Nitro*-4-*methoxy*-2-*methylbenzoic acid*. The methyl ether (1 g.) was refluxed with potassium permanganate (4 g.) in water (150 c.c.) for several hours, and excess of potassium permanganate reduced by a few drops of alcohol. The liquid was filtered hot, cooled, and acidified with hydrochloric acid. The white flocculent precipitate, recrystallised from water, gave clusters of microscopic needles, m. p. 235° (decomp.), identical with the substituted toluic acid of hitherto uncertain constitution obtained by Cain and Simonsen (*loc. cit.*) from 6-nitro-3 : 4-dimethylanisole. The toluic acid must have the –Me meta to the –OMe since this is the only acid which could be formed from a mononitro-4-acetyl-3-methylphenol. Cain and Simonsen's acid is therefore 5-nitro-4-methoxy-2-methylbenzoic acid, and the nitration product of 4-acetyl-3-methylphenol has the nitro-group in the 6-position.

6-*Amino*-4-*acetyl*-3-*methylphenol*. This was obtained by reduction of the nitro-compound (1·8 g.) in boiling alkaline solution with sodium dithionite (hydrosulphite). On neutralisation (with dilute acetic acid) 1 g. of *base* was obtained, in pale yellow prisms, m. p. 116° from alcohol (Found: N, 8·63. $C_9H_{11}O_2N$ requires N, 8·5%).

6-*Amino*-3-*methyl*-4-*ethylphenol*. The aminoacetylphenol (0·6 g.) was refluxed (2 hrs.) with amalgamated zinc (1·5 g.) and hydrochloric acid (10 c.c.; 1 : 1) with further additions of acid from time to time. The liquid was cooled, filtered, neutralised with ammonia, and extracted with ether. The ether extract was dried (Na_2SO_4) and the ether removed, yielding 6-*amino*-3-*methyl*-4-*ethylphenol* as a white, crystalline powder, m. p. 160° (decomp.) (Found: N, 9·2. $C_9H_{13}ON$ requires N, 9·3%).

The following were prepared similarly: 6-*nitro*-4-*propionyl*-3-*methylphenol*, pale greenish-yellow prisms from alcohol, m. p. 95° (Found: N, 6·7. $C_{10}H_{11}O_4N$ requires N, 6·7%); 6-*nitro*-3-*methyl*-4-*propylphenyl methyl ether*, white rectangular prisms from alcohol, m. p. 137° (Found: N, 6·33. $C_{11}H_{13}O_4N$ requires N, 6·3%); 6-*amino*-4-*propionyl*-3-*methylphenol*, pale brown prisms with domed ends, m. p. 135° (Found: N, 7·4. $C_{10}H_{13}O_2N$ requires N, 7·8%); 6-*amino*-3-*methyl*-4-n-*propylphenol*, white crystalline powder, m. p. 145° (decomp.) (Found: N, 8·1. $C_{10}H_{15}ON$ requires N, 8·5%).

The assistance of Messrs A. H. Daniel, D. G. Giles, and A. I. Osakwe with parts of the experimental work is acknowledged.

The author's thanks are also due to Dr. L. E. Sutton for much helpful criticism and to Professor Sir Robert Robinson, P.R.S., for his interest in this work.

DYSON PERRINS LABORATORY, OXFORD. [*Received, January 29th*, 1948.]

433. *Some Heterocyclic Analogues of Stilbenes.*

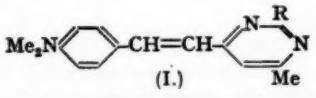
By Daniel M. Brown and George A. R. Kon.

Derivatives of 4-aminostilbene are known to be carcinogenic and also to exercise an inhibitory effect on the development of transplanted tumours in the rat. A number of analogous compounds, in which one benzene ring of the stilbene is replaced by a heterocyclic ring, are now described.

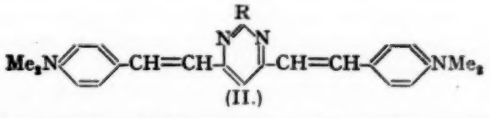
It has recently been found that a number of basically substituted stilbenes of the general type $NR_2 \cdot C_6H_4 \cdot CH{:}CH \cdot Ar$ are carcinogenic and possess the property common to many carcinogens of inhibiting the development of transplanted tumours in rats. A full account of this work has recently been published (*Phil. Trans.*, **1948**, *A*, **241**, 147). It appeared of interest to prepare for tests certain analogues of the biologically active stilbene, containing heterocyclic in place of the homocyclic nuclei.

As a preparative method, advantage was taken of the well-known reactivity of the methyl groups in certain positions of a variety of heterocyclic compounds (pyridine, quinoline, pyrimidine, etc.), whereby styryl derivatives are produced by condensation with aromatic aldehydes (cf., *e.g.*, Gabriel and Colman, *Ber.*, **1903**, **36**, 3383; Stark, *ibid.*, **1909**, **42**, 702; Stark and Bögemann, *ibid.*, **1910**, **43**, 1128).

Pyrimidine Derivatives.—4-Dimethylaminobenzaldehyde condenses smoothly with 4-methylpyrimidine in presence of zinc chloride, to give 4-(*4-dimethylaminostyryl*)*pyrimidine*. Stark and Bögemann (*loc. cit.*) have shown that 4-dimethylaminobenzaldehyde condenses with 2-hydroxy-4 : 6-dimethylpyrimidine in presence of catalytic amounts of piperidine in boiling ethanol to give 2-hydroxy-4-(4-dimethylaminostyryl)-6-methylpyrimidine (I; R = OH). We find that the reaction product also contains some *2-hydroxy-4 : 6-bis-(4-dimethylaminostyryl)pyrimidine* (II; R = OH). Analysis figures for this compound are only approximate and are more in accord with those calculated for the hemihydrate. This condensation takes place more rapidly in aqueous ethanol in presence of either catalytic or molecular quantities of hydrochloric acid and again gives a mixture of the mono- and bis-compounds (I and II; R = OH). Owing to the insoluble nature of the hydroxy-compounds purification on a large scale is difficult, so that the crude preparation of I (R = OH) is used for the preparation of *2-chloro-4-(4-dimethylaminostyryl)-6-methylpyrimidine* (I; R = Cl) together with some *2-chloro-4 : 6-bis-(4-dimethylaminostyryl)pyrimidine* (II; R = Cl). The latter is also obtained from the pure bis-compound which is prepared from 2-hydroxy-4 : 6-dimethylpyrimidine and 2 molecules of 4-dimethylaminobenzaldehyde in presence of either piperidine or hydrochloric acid. The chloro-compounds are readily separated by chromatography on alumina; this also constitutes an excellent method of purification.



(I.)



(II.)

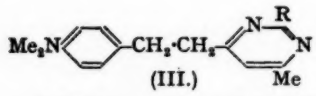
Heating 2-chloro-4-(4-dimethylaminostyryl)-6-methylpyrimidine (I; R = Cl) with a variety of amines affords 2-basically-substituted *pyrimidines* [I; R = piperidino-, morpholino-, *cyclo*hexylamino-, diethylamino-, 2-diethylaminoethylamino-, or bis-(2-hydroxyethyl)amino-] in high yield. No product can be isolated from the reaction with methanolic ammonia at 175°, and when this is carried out at 110° the starting material is recovered unchanged. However, *2-acetamido-4-(4-dimethylaminostyryl)-6-methylpyrimidine* (I; R = NHAc) is obtained in small yield from 4-dimethylaminobenzaldehyde and 2-amino-4 : 6-dimethylpyrimidine in boiling acetic anhydride.

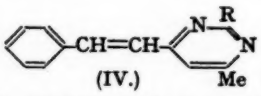
2-Chloro-4 : 6-bis-(4-dimethylaminostyryl)pyrimidine (II; R = Cl) reacts readily with piperidine to give *2-piperidino-4 : 6-bis-(4-dimethylaminostyryl)pyrimidine* (II; R = piperidino-).

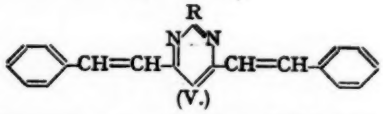
2-Ethoxy-4-(4-dimethylaminostyryl)-6-methylpyrimidine (I; R = OEt) is obtained from (I; R = Cl) with sodium ethoxide.

Attempts to dehalogenate (I; R = Cl) have not been successful. No reaction is observed on boiling a suspension of the chloro-compound with zinc dust in water (cf., *inter alia.*, Gabriel and Colman, *loc. cit.*) or in solution in aqueous dioxan. Hydrogenation at room temperature and pressure over 2% palladised strontium carbonate is rapid and gives only *2-chloro-4-[2-(4-dimethylaminophenyl)ethyl]-6-methylpyrimidine* (III; R = Cl). This reacts with piperidine to give *2-piperidino-4-[2-(4-dimethylaminophenyl)ethyl]-6-methylpyrimidine* (III; R = piperidino-)

identical with that prepared by hydrogenation over palladised strontium carbonate of 2-piperidino-4-(4-dimethylaminostyryl)-6-methylpyrimidine (I; R = piperidino-).


(III.)


(IV.)


(V.)

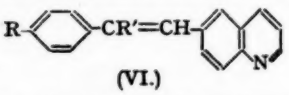
2-Hydroxy-4-styryl-6-methylpyrimidine (Stark and Bögemann, *loc. cit.*) gives 2-chloro-4-styryl-6-methylpyrimidine (IV; R = Cl) with phosphorus oxychloride. Treatment with piperidine affords *2-piperidino-4-styryl-6-methylpyrimidine* (IV; R = piperidino-). In the same way, from 2-hydroxy-4 : 6-distyrylpyrimidine (Stark and Bögemann, *loc. cit.*), *2-chloro-4 : 6-distyrylpyrimidine* (V; R = Cl) and *2-piperidino-4 : 6-distyrylpyrimidine* (V; R = piperidino-) are prepared.

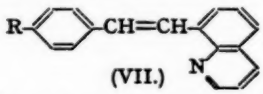
2-Piperidino-4 : 6-dimethylpyrimidine and 2 : 6-dipiperidino-4-methylpyrimidine, prepared from the corresponding chloro-compounds, fail to react with 4-dimethylaminobenzaldehyde under a variety of conditions. However, further work in progress in these laboratories should shed light on the effect of substituents on the condensations of aldehyde with methylpyrimidines.

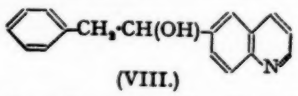
The results of the biological tests will be reported in detail elsewhere; the compounds (I; R = piperidino- or morpholino-) possess considerable growth-inhibitory action.

Styrylquinolines.—Condensation of 4-nitrophenylacetic acid with quinoline-6- and -8-aldehydes (Rodionov and Berkenheim, *J. Gen. Chem. Russia*, 1944, **14**, 330), by the method of Pfeiffer (*Ber.*, 1915, **48**, 179) leads to the formation of 6- and 8-(*4-nitrostyryl)quinoline* (VI; R = NO_2, R′ = H) and (VII; R = NO_2). Stannous chloride reduction (Pfeiffer and Seriewskaja, *Ber.*, 1911, **44**, 1110) gives the corresponding 6- and 8-(*4-aminostyryl)quinoline* (VI; R = NH_2, R′ = H), and (VII; R = NH_2).

Cook, Heilbron, and Steiger (*J.*, 1943, 413) failed to obtain *6-styrylquinoline* (VI; R = R′ = H) by the Meerwein reaction (Meerwein, Büchner, and van Emster, *J. pr. Chem.*, 1939, **152**, 237). In our hands the Grignard reaction between benzylmagnesium chloride and quinoline-6-aldehyde gives a very small yield of *2-phenyl-1-(6-quinolyl)ethanol* (VIII), together with unidentified resinous material. The condensation of quinoline-6-aldehyde with sodium


(VI.)

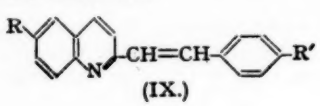

(VII.)

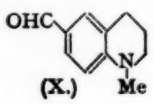

(VIII.)

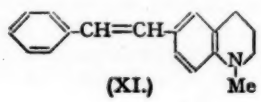
phenylacetate and acetic anhydride gives *α-phenyl-β-(6-quinolyl)acrylic acid* (VI; R = H, R′ = CO_2H) quantitatively, but we have not succeeded in decarboxylating it. A Skraup synthesis using 4-aminostilbene gives no recognisable product. The styrylquinoline is obtained, in poor yield, by deamination of 6-(4-aminostyryl)quinoline, by reduction of the diazonium salt with hypophosphorous acid (" Organic Reactions," Vol. II, 262).

The carcinogenicity of " styryl 430 " (Browning, Gulbransen, and Niven, *J. Path. Bact.*, 1936, **42**, 155), together with the tumour-inhibiting action of the closely related 6-acetamido-2-(4-aminostyryl)quinoline methoacetate (Badger, Elson, Haddow, Hewett, and Robinson, *Proc. Roy. Soc.*, 1942, *B*, **130**, 255), led us to synthesise some substituted 6-amino-2-styrylquinolines. 6-Nitro-2-styrylquinoline (Schmidt, *Ber.*, 1905, **38**, 3718) is reduced to *6-amino-2-styrylquinoline* (IX; R = NH_2, R′ = H) by stannous chloride in glacial acetic acid saturated with dry hydrogen chloride, and is characterised as the *acetyl* derivative (IX; R = NHAc, R′ = H). If tin and hydrochloric acid are used, 2-(2-phenylethyl)quinoline is obtained (Schmidt, *loc. cit.*).

Condensations of 6-nitroquinaldine (Hamer, *J.*, 1921, **119**, 1435) with 4-dimethylaminobenzaldehyde and 4-nitrobenzaldehyde in presence of zinc chloride give *6-nitro-2-(4-dimethylaminostyryl)quinoline* (IX; R = NO_2, R′ = NMe_2) and *6-nitro-2-(4-nitrostyryl)quinoline* (IX; R = R′ = NO_2) in almost quantitative yields. Reduction is best effected by stannous chloride in fuming hydrochloric acid, yielding *6-amino-2-(4-dimethylaminostyryl)quinoline* (IX; R = NH_2, R′ = NMe_2), characterised as the *acetyl* derivative (IX; R = NHAc, R′ = NMe_2) and 6-amino-2-(4-aminostyryl)quinoline (IX; R = R′ = NH_2), already prepared by Browning, Cohen, Cooper, and Gulbransen (*Proc. Roy. Soc.*, 1931, *B*, **109**, 51). The free amines are very sensitive to aerial oxidation.

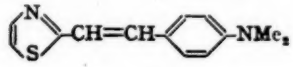

(IX.)


(X.)

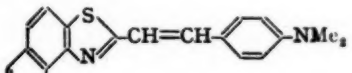

(XI.)

For the preparation of 6-*styryl*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydroquinoline* (XI), 6-*formyl*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydroquinoline* (X) was required. This is readily obtained by formylation of 1-methyltetrahydroquinoline (Feers and Koenigs, *Ber.*, 1885, **18**, 2389) by means of *N*-methylformanilide and phosphorus oxychloride in benzene (Vilsmeier and Haak, *Ber.*, 1927, **60**, 119). Quinoline fails to undergo a similar reaction (Cook, Heilbron, and Steiger, *loc. cit.*). The orientation of the formyl group is determined by Kishner–Wolff reduction to a dimethyltetrahydroquinoline and comparison of the picrate with that of the previously described 1 : 6-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoline (von Braun and Aust, *Ber.*, 1916, **49**, 509). The action of benzylmagnesium chloride on this aldehyde, followed by dehydration of the intermediate carbinol (not isolated), gives the required styryl compound.

Miscellaneous Styrylheterocycles.—Condensation of 2-methylthiazole with 4-dimethylaminobenzaldehyde in presence of zinc chloride gives 2-(4-*dimethylaininostyryl*)*thiazole* (XII). The yield of product in this condensation is very low and sometimes nil, and the analysis figures obtained are only approximate. Similarly, 2-methyl-β-naphthathiazole gives 2-(4-*dimethylaminostyryl*)-β-*naphthathiazole* (XIII). 2-Styrylbenzthiazole, previously prepared by Hofmann (*Ber.*, 1880, **13**, 1235) by heating cinnamic acid with *o*-aminothiophenol, and by Mills and Whitworth (*J.*, 1927, 2748) by the action of cinnamoyl chloride on the sodium salt of *o*-aminothiophenol, is made by heating 2-methylbenzthiazole with benzaldehyde in presence of concentrated hydrochloric acid (cf. Brooker and Sprague, *J. Amer. Chem. Soc.*, 1941, **63**, 3212). In the same way 2-(4-dimethylaminostyryl)-ββ′-naphthathiazole is prepared from its components; the condensation without catalyst described by Rupe and Schwarz (*Z. Farben u. Textil Chem.*, 1904, **3**, 397; *Chem. Zentr.*, 1905, I, 100) could not be repeated.



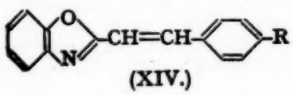
(XII.)



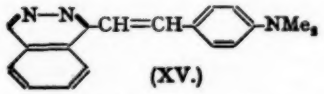
(XIII.)

2-(4-Dimethylaminostyryl)benziminazole (Rupe, Pedrini, and Collin, *Helv. Chim. Acta*, 1923, **15**, 1321) is readily prepared from *o*-phenylenediamine and 4-dimethylaminocinnamaldehyde in presence of cupric acetate by an extension of the method of Weidenhagen (*Ber.*, 1936, **69**, 2263).

There are many references to the condensation of quaternary salts of 2-methylbenzoxazole with aldehydes, in the preparation of cyanine-type dyes (*inter alia*, Brooker and White, *J. Amer. Chem. Soc.*, 1935, **57**, 2480). This, together with the fact that benzoxazole-2-carboxylic acid is readily decarboxylated (Skraup and Moser, *Ber.*, 1926, **59**, 1007), suggests that the 2-methyl group should be active and undergo condensation reactions. However, the condensation of the base itself has not been described. Skraup (*Annalen*, 1919, **419**, 85) prepared an oil, b. p. 325—335°, provisionally regarded as 2-styrylbenzoxazole (XIV; R = H), by heating *o*-aminophenol with cinnamamide. Subsequently Skraup and Moser (*loc. cit.*) attempted without success to condense 2-methylbenzoxazole with benzaldehyde in presence of piperidine at 250°. Dent (Thesis presented to the Graduate Faculty of the University of Cincinnati, 1942, 50, quoted from Bywater, Coleman, Kamm, and Merritt, *J. Amer. Chem. Soc.*, 1945, **67**, 905) obtained 2-styrylbenzoxazole (b. p. 193—194°/2 mm.; m. p. 79—80°). This publication is not available, so that the method of preparation is not known. Bywater *et al.* (*loc. cit.*) obtained the same compound (b. p. 220—221°/14 mm.; m. p. 83—84°) by heating together *o*-aminophenol and cinnamic acid; a by-product of unestablished structure isolated by these authors and characterised as the hydrochloride (m. p. 154—155°) was almost certainly 2-methylbenzoxazole. An authentic specimen of 2-*methylbenzoxazole hydrochloride* has m. p. 154°. We find that 2-methylbenzoxazole condenses readily with benzaldehyde in presence of zinc chloride to give 2-styrylbenzoxazole, m. p. 81—82° (*picrate*, m. p. 163—164°). Similarly condensation with 4-dimethylaminobenzaldehyde, under carefully controlled conditions, gives 2-(4-*dimethylaminostyryl*)*benzoxazole* (XIV; R = NMe_2).



(XIV.)

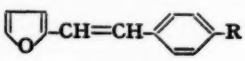


(XV.)

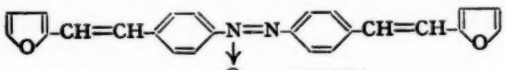
Heating 4-dimethylaminobenzaldehyde with 1-methylphthalazine in presence of zinc chloride affords 1-(4-*dimethylaminostyryl*)*phthalazine* (XV) in poor yield.

2-(4-*Nitrostyryl*)*furan* (XVI; R = NO_2) is prepared by condensation of furfuraldehyde and

4-nitrophenylacetic acid in presence of piperidine, and from diazotised *p*-nitroaniline and furylacrylic acid (Meerwein reaction). Reduction under acid conditions gives rise to resinous



(XVI.)



(XVII.)

products, while hydrogenation over Raney nickel at atmospheric pressure affords only the *azoxy*-compound (XVII). Reduction to 2-(4-*aminostyryl*)*furan* (XVI; R = NH_2) is readily accomplished by zinc dust and ammonium chloride in alcoholic solution, with evolution of heat. The amine darkens rapidly in the air, and gives an *acetyl* derivative (XVI; R = NHAc).

Experimental.

(Melting points are uncorrected.)

4-(4-*Dimethylaminostyryl*)*pyrimidine*.—4-Methylpyrimidine (1·0 g.; Gabriel and Colman, *Ber.*, 1899, **32**, 1525), 4-dimethylaminobenzaldehyde (1·5 g. = 1 mol.), and zinc chloride (fused; 0·5 g.) were heated in an oil-bath at 165° for 1·5 hours. The product was dissolved in dilute hydrochloric acid, the solution basified with ammonia, and the yellow precipitate collected and crystallised from ethanol. 4-(4-*Dimethylaminostyryl*)*pyrimidine* separated in yellow needles (1·2 g.), m. p. 179° (Found: C, 74·4; H, 6·6. $C_{14}H_{15}N_3$ requires C, 74·6; H, 6·7%). The *picrate* separated from methanol in purple, elongated prisms, m. p. 195—196° (transformation to long black needles at 175°) (Found: C, 53·0; H, 4·1. $C_{20}H_{18}O_7N_6$ requires C, 52·8; H, 4·0%).

Condensation of 2-*Hydroxy*-4 : 6-*dimethylpyrimidine and* 4-*Dimethylaminobenzaldehyde* (1 mol.).—(a) *Method of Stark and Bögemann* (loc. cit.). From the crude reaction product [m. p. 250—260° (decomp.)] was isolated, by several crystallisations from diethylene glycol (2 : 2′-dihydroxydiethyl ether), 2-*hydroxy*-4 : 6-*bis*-(4-*dimethylaminostytyl*)*pyrimidine*. It formed glistening purple leaflets, decomp. 316—318° (Found: C, 73·3, 73·0; H, 6·5, 6·4; N, 14·4. $C_{24}H_{26}ON_4$ requires C, 74·6; H, 6·8; N, 14·5. $C_{24}H_{26}ON_4,\frac{1}{2}H_2O$ requires C, 73·1; H, 6·9; N, 14·2%). Crystallisation of the more soluble fraction from 2-methoxyethanol yielded small scarlet platelets, m. p. 253° (decomp.) (Stark and Bögemann, *loc. cit.*, give m. p. 250—252° for the monostyryl compound). Attempts to separate the components of the reaction product by crystallisation of the hydrochloride or the sodium salt were unsuccessful.

(b) *Acid-catalysed condensation*. 4-Dimethylaminobenzaldehyde (1·5 g.), and 2-hydroxy-4 : 6-dimethylpyrimidine hydrochloride (1·5 g. = 1 mol.), dissolved in ethanol (20 c.c.) and water (10 c.c.), were heated at the boil for 4 hours, during which time a purple colour developed and solid material separated. After trituration with ammonia, the scarlet base was collected, washed well with water, ethanol, and ether, and dried; (1·4 g.), decomp. 313°, after softening and slow decomposition from 280°. Crystallisation from diethylene glycol yielded the characteristic purple leaflets of the bis-compound, decomp. 314—316°; the crude product, however, was a mixture of the hydroxy-mono- and -bis-compounds since treatment with phosphorus oxychloride gave both corresponding chloro-compounds (see below).

The same product was obtained when the reaction (12 hours) was catalysed by 1 drop of concentrated hydrochloric acid.

2-*Hydroxy*-4 : 6-*bis*-(4-*dimethylaminostyryl*)*pyrimidine*.—(*a*) 2-Hydroxy-4 : 6-dimethylpyrimidine (1·1 g.), 4-dimethylaminobenzaldehyde (3·0 g. = 2 mols.), and piperidine (10 drops) in ethanol (100 c.c.) were refluxed for 48 hours. After this time, small red platelets separated and were collected and crystallised from very much ethanol, forming small red platelets, decomp. 313—316°.

(*b*) 4-Dimethylaminobenzaldehyde (1·5 g.), 2-hydroxy-4 : 6-dimethylpyrimidine hydrochloride (0·75 g.), water (5 c.c.), and ethanol (20 c.c.) were heated, at the boil, overnight. Treatment with ammonia gave the free base as a red powder (1·22 g.). One crystallisation from diethylene glycol afforded glistening leaflets, decomp. 316—318° (Found: C, 73·1; H, 6·9%).

The crude product from the preparation of 2-hydroxy-4-(4-dimethylaminostyryl)-6-methylpyrimidine (I; R = OH) (2·0 g.) was refluxed with phosphorus oxychloride (10 c.c., freshly distilled) for 2 hours, or until all solid was in solution, excess of phosphorus oxychloride was removed under reduced pressure, and the residue was poured on ice. After making faintly alkaline with ammonia, the red precipitate was collected and dissolved in benzene–light petroleum, and the solution was dried (Na_2SO_4) and chromatographed on alumina. The orange band was eluted with the same solvent, and gave 2-*chloro*-4-(4-*dimethylaminostyryl*)-6-*methylpyrimidine*, which crystallised from benzene–light petroleum (b. p. 60—80°) in yellow leaflets (1·2 g.), m. p. 176—177° (Found: C, 65·9; H, 5·8. $C_{15}H_{16}N_3Cl$ requires C, 65·8; H, 5·9%). Further elution of the column with benzene–chloroform gave 2-*chloro*-4 : 6-*bis*-(4-*dimethylaminostyryl*)*pyrimidine*, also prepared from pure 2-hydroxy-4 : 6-bis-(4-dimethylaminostyryl)pyrimidine, separating from benzene in clusters of red platelets (0·1 g.), m. p. 223—224° (Found: C, 71·1; H, 6·2. $C_{34}H_{35}N_4Cl$ requires C, 71·3; H, 6·2%).

2-*Piperidino*-4 : 6-*bis*-(4-*dimethylaminostyryl*)*pyrimidine*.—2-Chloro-4 : 6-bis-(4-dimethylaminostyryl)pyrimidine (0·1 g.) was boiled with piperidine (1 c.c.) for 3 minutes. After addition of water (10 c.c.), the yellow *product* was collected and crystallised thrice from benzene–light petroleum (b. p. 60—80°). It separated in yellow prisms (0·025 g.), m. p. 223—224° (Found: C, 76·9; H, 7·6. $C_{33}H_{35}N_5$ requires C, 76·9; H, 7·8%).

2-*Piperidino*-4-(4-*dimethylaminostyryl*)-6-*methylpyrimidine*.—2-Chloro-4-(4-dimethylaminostyryl)-6-methylpyrimidine (0·52 g.) was boiled for 3 minutes with piperidine (2 c.c.), water (20 c.c.) added, and the *product* (0·6 g.) collected and dried. One crystallisation from light petroleum (b. p. 60—80°) gave light yellow platelets, m. p. 168—169° (Found: C, 74·5; H, 8·1. $C_{20}H_{24}N_4$ requires C, 74·3; H, 7·8%).

Boiling the chloro-compound with morpholine for 5 minutes and working up in the same way gave 2-*morpholino*-4-(4-*dimethylaminostyryl*)-6-*methylpyrimidine* (100%) which crystallised from light petroleum (b. p. 60—80°) as pale yellow needles, m. p. 155° (Found: C, 70·4; H, 7·3. $C_{19}H_{24}ON_4$ requires C, 70·4; H, 7·5%). Heating with *cyclo*hexylamine at 140—150° for 8 hours gave 2-cyclo*hexylamino*-4-(4-*dimethylaminostyryl*)-6-*methylpyrimidine* which separated from light petroleum (b. p. 60—80°) in bright yellow, flattened needles (82%), m. p. 142—143° (Found: C, 75·0; H, 8·4. $C_{21}H_{25}N_4$ requires C, 75·0; H, 8·4%).

2-Diethylaminoethylamine at 120° for 2½ hours gave 2-(2-*diethylaminoethylamino*)-4-(4-*dimethylaminostyryl*)-6-*methylpyrimidine* which crystallised from a little light petroleum (b. p. 60—80°) in clumps of yellow elongated prisms (65%), m. p. 80—81° (Found: C, 71·5; H, 8·8. $C_{21}H_{31}N_5$ requires C, 71·3; H, 8·8%). Diethylamine in a sealed tube at 130—140° for 5 hours gave 2-*diethylamino*-4-(4-*dimethylaminostyryl*)-6-*methylpyrimidine*, separating from a little light petroleum (b. p. 60—80°) in fine yellow needles (74%) or from aqueous ethanol in greenish-yellow laminae, m. p. 121—122° (Found: C, 73·4; H, 8·35. $C_{19}H_{26}N_4$ requires C, 73·5; H, 8·4%).

Diethanolamine at 140—150° for 3 hours gave 2-*bis*-(2-*hydroxyethyl*)*amino*-4-(4-*dimethylaminostyryl*)-6-*methylpyrimidine* which was recrystallised from aqueous ethanol to give small, bright yellow prisms, m. p. 116° (Found: C, 66·9; H, 7·7. $C_{19}H_{26}O_2N_4$ requires C, 66·7; H, 7·7%).

2-*Piperidino*-4-[2-(4-*dimethylaminophenyl*)*ethyl*]-6-*methylpyrimidine*.—2-Piperidino-4-(4-dimethylaminostyryl)-6-methylpyrimidine (1·0 g.) suspended in ethanol (50 c.c.) was rapidly hydrogenated at room temperature and pressure over 2% palladium–strontium carbonate catalyst. Removal of the catalyst by filtration through a layer of alumina and removal of solvent gave the *product* which crystallised from aqueous ethanol in colourless swords (0·8 g.), m. p. 70° (Found: C, 73·9; H, 8·4. $C_{20}H_{28}N_4$ requires C, 74·0; H, 8·7%).

2-*Ethoxy*-4-(4-*dimethylaminostyryl*)-6-*methylpyrimidine*.—The 2-chloro-compound (I; R = Cl) (1·0 g.), alcoholic sodium ethoxide [from sodium (0·085 g.) and dry ethanol (25 c.c.)], and benzene (10 c.c.) were refluxed on a steam-bath for 1½ hours. Sodium chloride was removed by filtration, and, after removal of solvent, the *product* (0·8 g.) was crystallised from light petroleum (b. p. 60—80°), affording orange leaflets, m. p. 120° (Found: C, 72·2; H, 7·2. $C_{17}H_{21}ON_3$ requires C, 72·0; H, 7·5%).

In attempts to dehalogenate 2-chloro-4-(4-dimethylaminostyryl)-6-methylpyrimidine, it (0·2 g.) was dissolved in dioxan (15 c.c.) and water (20 c.c.), and refluxed with zinc dust (2 g.) for 3 hours. Filtration and removal of solvent gave a residue which had m. p. 175° after crystallisation from ethanol, undepressed by admixture with the starting material.

The chloro-compound (0·2 g.) was hydrogenated in benzene–ethanol solution over 2% palladium–strontium carbonate. Removal of catalyst and solvent gave 2-*chloro*-4-[2-(4-*dimethylaminophenyl*)*ethyl*]-6-*methylpyrimidine*, separating from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 59—60° (Found: C, 64·9; H, 6·7. $C_{15}H_{18}N_3Cl$ requires C, 64·9; H, 6·6%). It reacted exothermically with piperidine to give a product which separated from aqueous ethanol in colourless flattened needles, m. p. 69° alone and admixed with 2-piperidino-4-[2-(4-dimethylaminophenyl)ethyl]-6-methylpyrimidine prepared by the other route.

2-*Chloro*-4-*styryl*-6-*methylpyrimidine*.—2-Hydroxy-4-styryl-6-methylpyrimidine (1·1 g.; Stark, *loc. cit.*) and phosphorus oxychloride (6 c.c.) were refluxed for 1 hour. The clear solution was poured on ice, and the gum which separated was extracted with benzene, and the solution dried and percolated through a short column of alumina. Elution with the same solvent and evaporation gave the product which crystallised from light petroleum in long, colourless, prismatic needles (0·35 g.), m. p. 95° (Found: C, 67·95; H, 4·9. $C_{13}H_{11}N_2Cl$ requires C, 67·6; H, 4·8%).

The above *chloro*-compound was refluxed with piperidine for 3 minutes, water was added, and the product which separated was collected and crystallised from aqueous ethanol. 2-*Piperidino*-4-*styryl*-6-*methylpyrimidine* separated in light yellow leaflets, m. p. 94° (Found: C, 77·6; H, 7·6. $C_{18}H_{21}N_3$ requires C, 77·4; H, 7·6%).

2-*Chloro*-4 : 6-*distyrylpyrimidine*.—2-Hydroxy-4 : 6-distyrylpyrimidine (2·5 g.; Stark, *loc. cit.*) and phosphorus oxychloride (13 c.c.) were refluxed for 5 hours. The clear solution was poured on ice, and the product extracted with benzene after neutralisation with ammonia. Three crystallisations from much ethanol (charcoal) gave long, colourless needles, m. p. 177—178° (Found: C, 75·2; H, 4·75. $C_{20}H_{15}N_2Cl$ requires C, 75·4; H, 4·74%).

2-*Piperidino*-4 : 6-*distyrylpyrimidine* was prepared as usual from the above *chloro*-compound (0·5 g.) and piperidine (3 c.c.). It separated from light petroleum (b. p. 60—80°) in light yellow, flattened needles (0·4 g.), m. p. 133° [Found (after drying at 120° in a high vacuum): C, 81·9; H, 6·8. $C_{25}H_{25}N_3$ requires C, 81·7; H, 6·9%].

2-*Piperidino*-4 : 6-*dimethylpyrimidine*, prepared from 2-chloro-4 : 6-dimethylpyrimidine (St. Angerstein, *Ber.*, 1901, **34**, 3959) and excess of piperidine, separated from aqueous ethanol in long, colourless, prismatic needles, m. p. 60—61° (Found: C, 69·1; H, 9·0. $C_{11}H_{17}N_3$ requires C, 69·05; H, 9·0%).

2 : 6-*Dipiperidino*-4-*methylpyrimidine*, prepared from 2 : 6-dichloro-4-methylpyrimidine (Gabriel and Colman, *loc. cit.*) and excess of piperidine, crystallised from aqueous ethanol in long, colourless needles or irregular laminae, m. p. 118° (Found: C, 69·4; H, 9·1. $C_{15}H_{24}N_4$ requires C, 69·2; H, 9·3%).

2-*Acetamido*-4-(4-*dimethylaminostyryl*)-6-*methylpyrimidine*.—2-Amino-4 : 6-dimethylpyrimidine (5·0 g.; Combes and Combes, *Bull. Soc. chim.*, 1892, **7**, 791) was refluxed for 5 minutes with acetic anhydride (15 c.c.). 4-Dimethylaminobenzaldehyde (6 g.; 1 mol.) in acetic anhydride (5 c.c.) was added, and the whole refluxed for 1 hour and then poured into water. After basification with sodium hydroxide, the solution was left overnight; the tarry product which had then solidified was boiled with much water, and the solid material was collected and crystallised several times from benzene and then from ethanol. The *product* separated in yellow needles (0·2 g.), m. p. 218—219° (Found: C, 68·8; H, 6·9. $C_{17}H_{20}ON_4$ requires C, 68·9; H, 6·8%).

6-(4-*Nitrostyryl*)*quinoline*.—Quinoline-6-aldehyde (5·0 g.; Rodionov and Berkenheim, *loc. cit.*), 4-nitrophenylacetic acid (5·8 g. = 1 mol.), and piperidine (2 c.c.) were heated under an air-condenser at

130—140° for 1½ hours. Cooling and stirring with acetic acid caused crystallisation of the *product* which was collected and recrystallised from aqueous acetic acid. It separated in yellow micro-needles (3·0 g.), m. p. 199—200° (Found: C, 73·8; H, 4·6. $C_{17}H_{12}O_2N_2$ requires C, 73·9; H, 4·4%).

8-(4-*Nitrostyryl*)*quinoline*.—Quinoline-8-aldehyde (6·75 g.), 4-nitrophenylacetic acid (7·8 g.), and piperidine were heated to 140° in an oil-bath and kept at that temperature for 1½ hours. The dark product was dissolved in chloroform, washed with sodium carbonate solution, then with water, and dried. The solution was percolated down a column of alumina (the top inch containing 50% of Norit), and the yellow band eluted with the same solvent. Removal of the solvent and crystallisation of the residue from benzene–light petroleum gave the *product* as yellow needles (2·3 g.), m. p. 171° (Found: C, 73·8; H, 4·6. $C_{17}H_{12}O_2N_2$ requires C, 73·9; H, 4·4%).

6-(4-*Aminostyryl*)*quinoline*.—To a solution of crystalline stannous chloride (16 g.) in glacial acetic acid (40 c.c.) saturated with dry hydrogen chloride, was added 6-(4-nitrostyryl)quinoline (powdered; 2·0 g.), and the solution stirred at room temperature for several hours. After being warmed on the steam-bath for 4 hours, the solution was cooled and the flocculent precipitate collected and boiled with water (300 c.c.) for 3 hours. After filtration and basification of the solution, the *product* was collected. It crystallised from chloroform in clusters of yellow platelets (0·87 g.), m. p. 214—215° (Found: C, 83·3; H, 6·0. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7%).

8-(4-*Aminostyryl*)*quinoline* was prepared as above from 8-(4-nitrostyryl)quinoline (0·5 g.). The tin complex was decomposed by boiling it with sodium carbonate solution. The *amine* crystallised from benzene–light petroleum in burrs of yellow, flattened needles (0·38 g.), m. p. 156° (Found: C, 82·9; H, 5·8. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7%).

2-*Phenyl*-1-(6-*quinolyl*)*ethanol*.—Quinoline-6-aldehyde (3·64 g.) in benzene (25 c.c.) was added to the Grignard reagent prepared from benzyl chloride (3·3 g.) and magnesium (0·62 g.) in ether (50 c.c.). A deep red flocculent precipitate separated immediately. After 2 hours' refluxing the mixture was decomposed with an ice-cold solution of ammonium chloride. The aqueous layer was extracted with benzene and the combined organic layers evaporated. The dark residual oil was dissolved in concentrated hydrochloric acid and extracted with ether. The acid layer was made alkaline and extracted with benzene. After removal of solvent the residue was distilled at 203°/0·1 mm. The distillate crystallised after treatment with a little methanol, and the *compound* separated finally from benzene–light petroleum in colourless needles (0·25 g.), m. p. 129·5—130° (Found: C, 82·2; H, 6·45. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·1%).

α-*Phenyl*-β-(6-*quinolyl*)*acrylic acid*.—Sodium phenylacetate (0·9 g.), quinoline-6-aldehyde (0·9 g.), acetic anhydride (5 c.c.), and zinc chloride (0·2 g.) were heated at 160° for 3 hours. The reaction mixture was poured into water and the colourless precipitate collected and dissolved in hot sodium carbonate solution. Undissolved oil was removed by extraction with benzene. The aqueous layer was acidified with acetic acid and the precipitate collected and dried (1·4 g.). One crystallisation from ethanol gave the pure *product* as a colourless crystalline powder, m. p. 265° (Found: C, 78·7; H, 4·9. $C_{18}H_{13}O_2N$ requires C, 78·5; H, 4·7%).

6-*Styrylquinoline*.—6-(4-Aminostyryl)quinoline (0·5 g.) dissolved in 5N-hydrochloric acid (2 c.c.) was diazotised at 0° with sodium nitrite (0·14 g.) in water (1 c.c.). The diazonium salt which separated was redissolved by adding water (3 c.c.) and, after addition of hypophosphorous acid (3 c.c. of 30% solution), the solution was left overnight at 0° and then at room temperature for 1 day. After basification with sodium hydroxide the product was extracted with benzene. It was purified by chromatography in light petroleum on alumina. 6-*Styrylquinoline* was eluted with benzene and crystallised from light petroleum, giving colourless platelets (10 mg.), m. p. 119° (Found: C, 88·3; H, 5·7. $C_{17}H_{13}N$ requires C, 87·8; H, 5·7%).

6-Nitroquinaldine was prepared by the method of Hamer (*loc. cit.*). Purification by chromatography in benzene on alumina and crystallisation from benzene–light petroleum gave colourless needles, m. p. 165° (described by Hamer, *loc. cit.*, as yellow needles, m. p. 164°).

6-*Amino*-2-*styrylquinoline* was prepared from 6-nitro-2-styrylquinoline (Schmidt, *loc. cit.*) by stannous chloride reduction as above. The tin complex was decomposed by hot sodium hydroxide solution and the amine extracted with chloroform. It separated from benzene–light petroleum in brown, sword-like prisms, m. p. 198—199° (Found: C, 82·8; H, 5·9. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7%). The *acetyl* derivative separated from chloroform with 1 molecule of chloroform of crystallisation in large colourless prisms, m. p. 193° (Found: C, 58·7; H, 4·0. $C_{19}H_{16}ON_2,CHCl_3$ requires C, 58·9; H, 4·2%). Crystallisation from aqueous ethanol afforded small colourless platelets, m. p. 193° (Found, after drying at 120°/2 mm.: C, 79·0; H, 5·6. $C_{19}H_{16}ON_2$ requires C, 79·2; H, 5·6%).

6-*Nitro*-2-(4-*dimethylaminostyryl*)*quinoline*.—6-Nitroquinaldine (5·0 g.), 4-dimethylaminobenzaldehyde (4·0 g.), and fused zinc chloride (0·2 g.) were heated at 160° for ½ hour. After cooling, the residue was dissolved in concentrated hydrochloric acid, and the solution diluted and basified with ammonia. The *product* was collected and crystallised from chloroform, separating in deep purple prismatic needles (7·6 g.), m. p. 248—249° (Found: C, 71·8; H, 5·5. $C_{19}H_{17}O_2N_3$ requires C, 71·5; H, 5·4%).

6-*Nitro*-2-(4-*nitrostyryl*)*quinoline*.—6-Nitroquinaldine (2·1 g.), 4-nitrobenzaldehyde (1·7 g.), and a little fused zinc chloride were heated at 170°. The melt frothed and rapidly solidified to a yellow mass; this was almost insoluble in benzene or chloroform, but a sample crystallised from much glacial acetic acid in clusters of yellow needles, m. p. 278° (Found: C, 63·7; H, 3·6. $C_{17}H_{11}O_4N_3$ requires C, 63·5; H, 3·5%).

6-*Amino*-2-(4-*dimethylaminostyryl*)*quinoline*.—The corresponding nitro-compound (IX; R = NO_2, R′ = NMe_2) (2·0 g.), crystalline stannous chloride (10·0 g.), and fuming hydrochloric acid (15 c.c.) were warmed on a steam-bath for 1 hour. The tin complex was collected, dissolved in hot water, and decomposed with excess of 10N-sodium hydroxide. The yellow precipitate was collected, well washed with water, and crystallised from methanol. The *amine* separated in brown needles (1·15 g.), m. p. 251—252° (Found: C, 79·0; H, 6·7. $C_{19}H_{19}N_3$ requires C, 78·9; H, 6·6%). The *acetyl* derivative, prepared by heating the amine with acetic anhydride and 1 drop of sulphuric acid at 100° for ½ hour, separated from aqueous methanol in orange-yellow needles, m. p. 241—242° (Found: C, 76·0; H, 6·5. $C_{21}H_{21}ON_3$ requires C, 76·1; H, 6·4%).

6-Amino-2-(4-aminostyryl)quinoline was prepared as above from the corresponding dinitro-compound (IX; R = R' = NO_2) (1·0 g.). It crystallised from aqueous methanol in yellow needles (0·6 g.), m. p. 242—243° (Browning *et al.*, *loc. cit.*, give m. p. 241—242°) (Found: C, 77·9; H, 5·7. Calc. for $C_{17}H_{15}N_3$: C, 78·1; H, 5·8%).

6-*Formyl*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydroquinoline*.—Phosphorus oxychloride (10·5 g.; 6·5 c.c.) and *N*-methylformanilide (9·2 g.) were dissolved in benzene (10 c.c.), and the solution left at room temperature for 1 hour and cooled to 0°. *N*-Methyltetrahydroquinoline (10 g.) was added dropwise with shaking, and the solution left overnight at room temperature, then poured on ice, basified with sodium hydroxide, and steam distilled. The residue was extracted with ether and the *product* purified through the bisulphite compound. It distilled at 219—221°/15 mm., and crystallised on standing to form large colourless plates (5·5 g.), m. p. 28—29° (Found: C, 75·4; H, 7·5. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·5%). The aldehyde (1 g.), hydrazine hydrate (100 c.c.; 2·25 c.c.), and ethanolic sodium ethoxide [16 c.c.; containing sodium (0·8 g.)] were heated in a sealed tube at 170—180° for 8 hours. Water (3 c.c.) was added to the contents of the tube, and most of the alcohol removed by distillation. The residue was diluted with water (20 c.c.) and extracted with ether (30 c.c.), and the ether extract washed (3 times) with water and dried. To a sample (2 c.c.) of this solution were added a few drops of saturated ethanolic picric acid. The picrate separated in light yellow plates, m. p. 150—152°. One recrystallisation from ethanol–ether gave yellow prisms, m. p. 152° (Found: N, 14·1. Calc. for $C_{17}H_{19}O_7N_4$: N, 14·4%). The picrate of authentic 1 : 6-dimethyltetrahydroquinoline has m. p. 152° (von Braun and Aust, *loc. cit.*).

6-*Styryl*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydroquinoline*.—To a Grignard reagent from benzyl chloride (1·23 g.) and magnesium (0·25 g.) in ether (30 c.c.) was added, dropwise and with shaking, a solution of formylmethyltetrahydroquinoline (1·53 g.) in benzene (25 c.c.). The solution was refluxed for 45 minutes on the water-bath, during which time a yellow complex separated. After standing at room temperature for 2 hours the reaction mixture was decomposed with saturated ammonium chloride solution and the organic layer separated. The aqueous layer was extracted with ether, and the combined organic layers evaporated to dryness. The residue was dissolved in benzene (25 c.c.) and refluxed with phosphoric oxide (2 g.) for 45 minutes. After decomposition with water and basification with 2N-sodium hydroxide, the benzene layer was separated, washed, dried, diluted with an equal volume of light petroleum, and chromatographed on alumina. Elution with the same solvent and crystallisation from light petroleum (b. p. 60—80°) gave the *product* as fine colourless needles (0·6 g.), m. p. 93—94° (Found: C, 86·6; H, 7·6. $C_{18}H_{19}N$ requires C, 86·7; H, 7·7%).

2-(4-*Dimethylaminostyryl*)*thiazole*.—2-Methylthiazole (1 c.c.), 4-dimethylaminobenzaldehyde (1·5 g.), and zinc chloride (fused; *ca.* 0·5 g.) were heated in a sealed tube at 160—170° for 14 hours. The product was dissolved in dilute hydrochloric acid, and the solution basified with ammonia and extracted with benzene. Chromatography of the extract on alumina and then two crystallisations from light petroleum (b. p. 40—60°) gave the *product* as yellow laminae (10 mg.), m. p. 124° (Found: C, 68·5; H, 6·0. $C_{13}H_{14}N_2S$ requires C, 67·8; H, 6·1%).

2-(4-*Dimethylaminostyryl*)-*β*-*naphthathiazole* was prepared as above by heating 2-methyl-*β*-naphthathiazole (0·5 g.), 4-dimethylaminobenzaldehyde (0·4 g.), and zinc chloride (0·5 g.) at 160—180° for 1½ hours. It crystallised from light petroleum (b. p. 60—80°) in the form of yellow swords (0·3 g.), m. p. 170—171° (Found: C, 76·6; H, 5·7. $C_{21}H_{18}N_2S$ requires C, 76·3; H, 5·5%).

2-*Styrylbenzthiazole*.—2-Methylbenzthiazole (1 g.), benzaldehyde (freshly distilled; 0·8 c.c.), and 2 drops of concentrated hydrochloric acid were heated overnight at 100° in a sealed tube. The product was worked up as above, and separated from ethanol in colourless needles (0·46 g.), m. p. 112°; Mills and Whitworth (*loc. cit.*) give m. p. 112—113°.

2-(4-Dimethylaminostyryl)-*ββ'*-naphthathiazole was prepared in the same way as 2-styrylbenzthiazole from 2-methyl-*ββ'*-naphthathiazole (0·5 g.). It crystallised from benzene–light petroleum (b. p. 60—80°) in yellow needles (0·33 g.), m. p. 217—218° (Rupe and Schwarz, *loc. cit.*, give m. p. 212°).

2-(4-*Dimethylaminostyryl*)*benziminazole*.—Solutions of *o*-phenylenediamine (2·2 g.) in methanol (50 c.c.), cupric acetate (8 g.) in water (100 c.c.), and 4-dimethylaminocinnamaldehyde (3·5 g.) in warm methanol (50 c.c.) were mixed and warmed on a steam-bath for 1 hour. After cooling, the brown precipitate was collected, washed with aqueous methanol, and suspended in 50% methanol (200 c.c.). Hydrogen sulphide was passed into the solution (2 hours). After filtration, the filtrate and washings were evaporated and the residue crystallised from methanol–ethanol. 2-(4-Dimethylaminostyryl)benziminazole separated in long orange prismatic needles (1·0 g.), m. p. 258° (Rupe *et al.*, *loc. cit.*, give m. p. 256°).

2-*Methylbenzoxazole hydrochloride*, prepared by passing dry hydrogen chloride into an ether solution of 2-methylbenzoxazole, separated from ethanol–ether in large colourless prisms, m. p. 154° (Found: C, 56·7; H, 4·8. C_8H_8ONCl requires C, 56·7; H, 4·8%).

2-*Styrylbenzoxazole*.—2-Methylbenzoxazole (2 c.c.), freshly distilled benzaldehyde (2 c.c.), and anhydrous zinc chloride (powdered; 1 g.) were heated in a sealed tube at 160° for 6 hours. The product was steam distilled until the distillate was clear, and the residue was made acid with hydrochloric acid and then basified with ammonia. The oil which separated rapidly solidified. It was purified by chromatography in benzene–light petroleum on alumina, and crystallised from light petroleum (b. p. 60—80°) in colourless needles (1 g.), m. p. 81—82° (Found: C, 81·8; H, 5·2. Calc. for $C_{15}H_{11}ON$: C, 81·5; H, 5·0%). The *picrate* separated from benzene–light petroleum in fine yellow needles, m. p. 163—164° (Found: C, 55·8; H, 3·2. $C_{15}H_{11}ON,C_6H_3O_7N_3$ requires C, 56·0; H, 3·1%).

2-(4-*Dimethylaminostyryl*)*benzoxazole* was obtained in the same way from 2-methylbenzoxazole (1·0 g.), 4-dimethylaminobenzaldehyde (1·12 g.), and fused zinc chloride (0·5 g.) overnight at 160°. It separated from benzene–light petroleum (b. p. 60—80°) in the form of yellow glistening leaflets (0·35 g.), m. p. 174—175° (Found: C, 77·2; H, 6·3. $C_{17}H_{15}ON_2$ requires C, 77·2; H, 6·1%).

1-(4-*Dimethylaminostyryl*)*phthalazine*.—1-Methylphthalazine (Gabriel and Eschenbach, *Ber.*, 1897, **30**, 3026) (2·5 g.), 4-dimethylaminobenzaldehyde (2·75 g.), and fused zinc chloride (0·75 g.) were heated in an oil-bath at 160° for 2 hours. After solution of the reaction mixture in dilute hydrochloric acid and basification with ammonia, the product was extracted with benzene. It was purified by percolation of the solution through a column of alumina (Savory and Moore, " Brockmann "; a more alkaline alumina

caused rapid decomposition of the product) and elution with benzene containing a few drops of methanol. 1-(4-*Dimethylaminostyryl*)*phthalazine* formed flattened orange needles (0·39 g.), m. p. 186—187° from benzene–light petroleum (Found: C, 78·3; H, 6·2. $C_{18}H_{17}N_3$ requires C, 78·5; H, 6·2%).

2-(4-*Nitrostyryl*)*furan* (Preparation by Dr. R. J. C. Harris).—(*a*) Furfuraldehyde (5·0 g.), 4-nitrophenylacetic acid (9·0 g.), and piperidine (1 c.c.) were heated at 130—140° for 5 hours. The black resinous product was extracted with hot benzene, and the extract washed with 2N-hydrochloric acid, sodium carbonate solution, and water, and dried. The solution was chromatographed on a column of alumina (75 g.), and the 2-(4-*nitrostyryl*)*furan* eluted with benzene. Evaporation of the eluate gave orange needles (2·0 g.), m. p. 130—131° from ethanol (Found: C, 66·95; H, 4·4. $C_{12}H_9O_3N$ requires C, 67·0; H, 4·2%).

(*b*) A mixture of *p*-nitroaniline (17·25 g.), 25% hydrochloric acid (50 g.), and ice (50 g.) was diazotised with a solution of sodium nitrite (9 g.) in water (15 c.c.). The diazonium salt solution was filtered and added to a solution of furylacrylic acid in acetone (150 c.c.). The solution was vigorously stirred, and sodium acetate (27·5 g.) and cupric chloride (5·35 g.) in water (15 c.c.) were added. After 2 hours the mixture was steam distilled, and the residue treated as in (*a*). Yield 5·0 g., m. p. 130—131°.

Reduction of 2-(4-*Nitrostyryl*)*furan*.—(*a*) The nitro-compound (0·5 g.) in ethyl acetate (30 c.c.) was shaken in hydrogen with Raney nickel (0·5 g.) at room temperature and pressure. After 1 hour, hydrogen uptake ceased and the catalyst and solvent were removed. The residue of brown needles was chromatographed in benzene on alumina, and the product crystallised from benzene. The *azoxy*-compound formed fine, orange needles, m. p. 231—232° (decomp.) (Found: C, 75·34; H, 4·9. $C_{24}H_{18}O_3N_2$ requires C, 75·36; H, 4·7%).

(*b*) The nitro-compound (1·0 g.), ammomium chloride (1·0 g.), zinc dust (4·0 g.) and ethanol (30 c.c.) containing water (3 c.c.) were refluxed on a steam-bath for 1 hour. The solution was filtered and diluted considerably with water; an almost colourless precipitate of fine needles then separated. This was collected and recrystallised from aqueous ethanol (charcoal), giving 2-(4-*aminostyryl*)*furan* in colourless needles, m. p. 104°. For analysis the compound crystallised from light petroleum in small colourless swords (Found: C, 77·8; H, 5·7. $C_{12}H_{11}ON$ requires C, 77·8; H, 6·0%). The *acetyl* derivative, prepared by boiling the amine for a few minutes with acetic anhydride, separated from aqueous ethanol in fine colourless needles, m. p. 201—202° (Found: C, 74·4; H, 6·0. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·8%).

The authors wish to thank the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, and the Anna Fuller Fund for grants made to the Royal Cancer Hospital in aid of this work, and are also indebted to Messrs Kodak Ltd and Imperial Chemical Industries Ltd. for gifts of chemicals.

The Chester Beatty Research Institute,
The Royal Cancer Hospital,
Fulham Road, London, S.W.3.

[*Received, January* 31*st*, 1948.]

---

434. *Some Catalysed Gas-phase Reactions of Aromatic Hydrocarbons. Part IV. The Polymethylbenzenes formed in the Reactions of Dimethyl Ether with Benzene, Toluene, and the Xylenes.*

By P. H. Given and D. Ll. Hammick.

The yields and isomeric compositions of the methylbenzenes formed in the methylation of benzene by dimethyl ether over a heated alumina–silica catalyst have been determined. All of the twelve possible isomers, with perhaps the exception of pentamethylbenzene, are formed; a little ethylbenzene is found in the xylene fractions. The corresponding reactions of toluene, *o*-, and *p*-xylene, and a xylene mixture, have also been investigated. Monomethylation is the predominating reaction in all cases, and the yields of polymethylated products fall off rapidly with the number of groups introduced. The compositions of the di- and tri-methylbenzene fractions are shown to correspond closely to the respective thermodynamic equilibrium mixtures. The process is compared with the liquid-phase Friedel–Crafts reaction.

It has been shown (Given and Hammick, *J.*, 1947, 928) that benzene interacts with dimethyl ether on the surface of metal oxide catalysts to yield toluene, xylene, and higher methylbenzenes. Other workers (for references, see Part I, *loc. cit.*) have reported similar gas-phase reactions, but the composition of the polymethylbenzenes formed in such processes has apparently not been investigated. It was therefore thought of interest to determine the yields of the polymethylbenzenes formed in the reaction of benzene, toluene, and each of the three xylenes with dimethyl ether in the presence of an alumina–silica catalyst, and to obtain information concerning the isomeric composition of the C_8, C_9, and C_{10} fractions.

Experimental.

Materials.—The preparation of the benzene, dimethyl ether, and synthetic alumina–silica catalyst ($Al_2O_3 : SiO_2 = 1 : 4$) has been described (Part I, *loc. cit.*).

Toluene. The collected toluene fractions from a number of previous methylations of benzene were fractionated twice through a Podbielniak still; b. p. 110·5°, $n_D^{20°}$ 1·4970.

o-*Xylene.* A sample of " pure " *o*-xylene was fractionated once in a Podbielniak still; b. p. 143·5—144°, $n_D^{20°}$ 1·5020, f. p. −28° (cf. values of 144·4°, 1·5052, and −25·2° respectively given by Forziati, Glasgow, Willingham, and Rossini, *J. Res. Nat. Bur. Stand.*, 1946, **36**, 129).

Mixture of xylene isomers (*mainly* m-). Commercial xylene ($n_D^{20°}$ 1·4925) was freed from sulphur compounds by washing with sulphuric acid, and was then fractionally distilled. The portion of b. p. 137—140° was boiled with dilute nitric acid and freed from aliphatic impurities by sulphonation and separation of unsulphonated material; the hydrocarbon was regenerated by hydrolysis of the acid, and was redistilled.* The analysis of the product (by ultra-violet spectroscopic method †) was: ethylbenzene, 0·0%; *p*-xylene, 15·7%; *m*-, 73·2%; *o*-, 11·1%.

p-*Xylene.* A sample of " pure "-grade hydrocarbon was twice partially frozen, the unfrozen residue being neglected; f. p. 13·2°, $n_D^{20°}$ 1·4959. Spectroscopic analysis showed the material to be at least 99·4% pure.

Experimental Method.—The apparatus and procedure were as described in Part I with the following exceptions: (1) Although the benzene was vapourised by electrical heating as in the previous work, the other hydrocarbons were boiled into the stream of methyl ether over a gas micro-burner. The rate of flow was calculated from the total weight of liquid passed, and the total time of the experiment. (2) The products of the methylation of toluene and the xylenes were immediately fractionated in the Podbielniak still, without the preliminary concentration of the products made in the earlier work.

Between 60 and 150 g. of toluene and the xylenes were passed over the catalyst in each run; but in order to obtain a reasonably large volume of the higher homologues for adequate investigation, 1000 g. of benzene were treated in one run.

Analysis of the Products.—The yields of the sets of C_7, C_8, C_9, and C_{10} hydrocarbons were determined by distillation in the Podbielniak still, which consisted of a vacuum-jacketed column 1 m. long and 0·55 cm. in diameter, packed with a wire spiral. Direct tests with known mixtures showed that the sets of C_7, C_8, C_9, and C_{10} hydrocarbons could be separated in the still with a maximum uncertainty in the analysis of ±0·3 c.c. The weight of starting material used in the various experiments was such that this uncertainty in the volumes resulted in a maximum uncertainty of about 4% in the percentages of C_7, C_8, and C_9 cuts in Table I, and about 10% in the C_{10} cuts; the uncertainty in many of the figures is considerably less than the maximum.

The penta- and hexa-methylbenzenes were determined by difference; some information about their relative proportions was obtained by the distillation of the collected high-boiling residues from a number of previous methylations of benzene.

Analyses of the C_8 and C_9 hydrocarbons obtained by methylation of benzene have been made spectroscopically; and the recovered xylene fractions from the xylene methylations have been analysed in the same way. In addition, the C_8 and C_9 cuts from every run were carefully refractionated to effect a partial separation between the isomers (a complete separation cannot be achieved in the type of Podbielniak still used). The b. p.s and f. p.s, and the m. p.s if above −78°, and also the refractive indices of the fractions, were determined. These data provided some further and confirmatory information.

In the analysis of the tetramethylbenzenes, use was made of the freezing point–composition curve for the binary system, durene–*iso*durene, reported by Smith and Macdougall (*J. Amer. Chem. Soc.*, 1929, **51**, 3001). The semi-solid distillate from the primary analysis was filtered off and sucked dry, and the weights of durene on the filter and of the liquid in the filter-flask were observed. Using the solubility of durene in *iso*durene at the temperature of the filtration estimated from the freezing-point curve, the total weight of durene was then calculated (the presence of a small amount of prehnitene should not affect the solubility greatly). The filtrates from the products of all methylation experiments described below were mixed, cooled to −15° to remove a further quantity of durene, and distilled through the Podbielniak still. An estimate of the average proportions of the three tetramethylbenzenes was thus obtained.

Results.—The yields of the sets of methylbenzenes obtained in the various experiments, expressed as moles of product per 100 moles of reactant passed, are given in Table I. The volume of the packed catalyst space was 470 c.c., and it contained 294 g. of catalyst.

The xylenes. The spectroscopic analyses of the C_8 cuts are given in Table II. All the xylene fractions obtained (including those recovered from the methylations of a single isomer) had a refractive index $n_D^{20°}$ 1·4979—1·4981, and all except that recovered from the methylation of the *o*-isomer showed similar behaviour on refractionation. The initial f. p. of the recovered *p*-xylene was −20°, and the other samples began to freeze at about −40° to −50°; none of the fractions was completely frozen at −75°.

The trimethylbenzenes. Spectroscopic analysis of the trimethylbenzenes from the methylation of benzene gave the following results: 1 : 3 : 5-isomer, 20·6%; 1 : 2 : 4-, 59·5%; 1 : 2 : 3-, 19·1%. The refractionation of the trimethylbenzene fractions from the various methylations showed that they were all of similar composition, that ψ-cumene was the main constituent, but that the other two isomers were both present. The data in Table III, relating to the trimethylbenzenes formed in the methylation of *p*-xylene, are typical specimens of the results.

The tetramethylbenzenes. The yields of durene, as percentages of the total C_{10} cut, are given below:

Substance methylated	Benzene.	*p*-Xylene.	*m*-Xylene.	*o*-Xylene.
Durene, % by weight	56	34	53	42

* The method of purification was that of Clarke and Taylor (*J. Amer. Chem. Soc.*, 1923, **45**, 831), who have claimed that it yields pure *m*-xylene from the commercial mixture.

† The authors wish to acknowledge gratefully the kindness of Dr. Powell of Anglo-Iranian Oil Co. Ltd., in performing all the spectroscopic analyses quoted in this paper. His method is described by Gordon and Powell, *J. Inst. Pet.*, 1945, **31**, 428.

TABLE I.

Reactant:	Benzene.	Toluene.			Xylenes:		
					p.	*o*.	mixture (mainly *m*).
Run.	1.	2.	3.	4.	5.	6.	7.
Rate of flow of hydrocarbon, g./hr.	29·6	33·6	42·5	50	60	51·5	51·5
Rate of flow of ether, g./hr.	10·9	15·3	15·3	15·3	15·3	15·3	15·3
Flow of hydrocarbon, vol. liq./vol. catalyst/hr.	0·072	0·082	0·10	0·12	0·15	0·13	0·13
Mol. ratio, hydrocarbon/ether ...	1·6	1·1	1·4	1·6	1·7	1·5	1·5
Yields (moles %).							
Benzene	61	3·0	2·6	—	0	0	0·4
Toluene	11·6	—	—	—	4·7	3·9	3·8
Xylene	3·9	22·3	20·8	19·0	52	51	54·4
Trimethylbenzene	1·6	8·7	7·9	6·2	22·1	21·9	23·4
Tetramethylbenzene	0·3	1·05	0·8	1·2	6·1	6·0	6·8
Penta- + hexa-methylbenzene ...	0·4	2·2	1·7	1·4	3·6	3·6	3·0
Total methylation per pass (%) ...	15·8	34·3	31·2	27·8	31·8	29·5	33·2
Monomethylated product calc. on hydrocarbon consumed *	29·7	—	—	—	46	45	51

* The "hydrocarbon consumed" is the difference between hydrocarbon passed and hydrocarbon recovered.

TABLE II.

Substance methylated.	Weight, %, of: C_6H_5Et.	p-$C_6H_4Me_2$.	m-$C_6H_4Me_2$.	o-$C_6H_4Me_2$.
Benzene	0·4	24·2	54·3	21·1
p-Xylene	0·8	33·8	46·1	19·3
m-Xylene	3·0	23·2	52·6	21·4
o-Xylene	0	17·0	45·6	37·4

TABLE III.

Distillation of trimethylbenzenes from p-*xylene.*

Fraction.	Vol., c.c.	B.p.	$n_D^{20°}$.	Fraction.	Vol., c.c.	B.p.	$n_D^{20°}$.
1	2·0	165—169°	1·5024	3	3·8	170—172°	1·5064
2	25·0	169—170	1·5040				

Fraction 2 froze within the range −58° to −69°.

The durene, crystallised twice from alcohol, had m. p. 79°. The combined liquids after removal of the solid durene were fractionated with the results given in Table IV.

TABLE IV.

Distillation of combined liquid tetramethylbenzenes.

Fraction.	Vol., c.c.	B.p.	F.p.	M.p.	$n_D^{20°}$.	Fraction.	Vol., c.c.	B.p.	F.p.	M.p.	$n_D^{20°}$.
1	3·3	194—198°	—	—	1·5124	3	4·2	198—199°	−16°	−35°	1·5138
2	4·7	198	—	—	1·5131	4	3·4	199—203	−11	−35	1·5149

Comparison of these figures with the data for the pure tetramethylbenzenes (see Smith *et al.*, *J. Amer. Chem. Soc.*, 1932, **54**, 1614, and references given therein; Francis, *Chem. Reviews*, 1948, **42**, 107) shows, after durene has been removed, the residue is mainly *iso*durene, but some prehnitene is present.

It can be estimated that the average composition of the various tetramethylbenzene fractions is: durene (1 : 2 : 4 : 5), 50%; *iso*durene (1 : 2 : 3 : 5), 42%; prehnitene (1 : 2 : 3 : 4), 8%.

Penta- and hexa-methylbenzenes. As stated above, no attempt was made to determine these substances directly in the routine analyses of the reaction products. The presence of hexamethylbenzene was demonstrated in the following manner. The residues from the analyses of the products of a number of methylations of benzene were distilled without a fractionating column. The temperature rose rapidly to 260° without pausing at either 232° or 255° (the b. p.s of pentamethylbenzene and diphenyl, respectively). A liquid distilled at 260—265°, and rapidly solidified in the condenser. The solid was crystallised from alcohol, m. p. 164—165° (corr.) (Found: C, 88·8; H, 11·1. Calc. for $C_{12}H_{18}$: C, 88·8; H, 11·2%). Hence the residual reaction products, after removal of the C_6 to C_{10} hydrocarbons, consist mainly of hexamethylbenzene; little, if any, pentamethylbenzene is formed. Diphenyl, which could conceivably be formed in side reactions, evidently is not present to any significant extent.

DISCUSSION.

The spectroscopic analyses given in Table II show that small amounts of ethylbenzene were present in the C_8 cuts recovered from the methylations of benzene, *p*-xylene, and the xylene

mixture. The benzene and toluene used in our experiments were carefully fractionated before use, and contained no ethylbenzene, and spectroscopic analyses of the *p*-xylene and the xylene mixture showed the absence of this hydrocarbon initially. (The spectroscopic analysis of the C_8 products of the methylation of the *o*-isomer revealed no ethylbenzene, so that the purity of the starting material is not in question in this case.)

Taylor, Wagman, Williams, Pitzer, and Rossini (*J. Res. Nat. Bur. Stand.*, 1946, **37**, 95) have calculated the equilibria among the four C_8 hydrocarbons in the vapour state over the temperature range, 298·16—1500° K.; it may be shown from their data that at 723° K. (450° C.) the equilibrium mixture contains: 9% ethylbenzene; 21·2% *p*-xylene; 47·3% *m*-; 22·5% *o*-. Comparison of these figures with the experimentally determined compositions of the C_8 cuts given in Table II shows that the proportion of *m*-xylene in all the four samples analysed agrees with the equilibrium value within the limits of experimental error; so also do the proportions of *o*- and *p*-xylene in the cuts separated from the methylations of benzene and the xylene mixture (the latter contained initially 73·2% *m*-, 11·1% *o*-, and 15·7% *p*-xylene). It is evident that *o*- and *p*-xylene do not isomerise all the way to the equilibrium mixture in a single passage over the catalyst (under our conditions) since the recovered fractions contain the respective starting materials in greater than equilibrium proportions. The proportion of ethylbenzene found is in all cases less than the equilibrium value; but one would perhaps expect the rate of isomerisation of one xylene into another to be much higher than the rate of isomerisation of a xylene into ethylbenzene.

Thus we conclude that the C_8 cut obtained as a product of the interaction of benzene and dimethyl ether under the conditions we have used is substantially the thermodynamic equilibrium mixture; and under the same conditions any xylene isomerises to a considerable extent towards the equilibrium mixture.

Rossini *et al.* (*loc. cit.*) have also calculated the equilibria among the eight C_9H_{12} alkylbenzenes in the gas phase at temperatures of 298·16—1500° K. From their data we may deduce that the proportions of the three trimethylbenzenes in equilibrium with each other would be: mesitylene (1 : 3 : 5), 22·0% ψ-cumene (1 : 2 : 4), 62·3%; hemimellitene (1 : 2 : 3), 15·7%. The trimethylbenzenes formed in the methylation of benzene had substantially this composition, within the limits of experimental error. Sufficient data are not available for a similar comparison to be instituted for the tetramethylbenzenes.

A comparison of the products of the gas-phase reaction described here with those of the liquid-phase Friedel–Crafts reaction may be made. In the former, the yield of the product formed by the introduction of one methyl group into toluene or xylene is about double the yield of the corresponding reaction of benzene (see Table I). Nevertheless, introduction of only one methyl group is the predominating reaction whatever the starting material, and the yields of polymethylbenzenes fall off rapidly with the number of groups introduced; the ratio of mono- to poly-methylation is rather insensitive to variations in the hydrocarbon : dimethyl ether ratio (see Part I, *loc. cit.*, p. 932). On the other hand, Smith and Dobrolovny (*J. Amer. Chem. Soc.*, 1926, **48**, 1413) found that in the Friedel–Crafts reaction of methyl chloride with xylene in the presence of aluminium chloride, the yield of disubstituted was high compared with monosubstituted products, whatever the proportion of methylating agent used; and considerably more penta- than hexa-methylbenzene was formed. The first of these results is a well-known characteristic of the Friedel–Crafts reaction (see Calloway, *Chem. Reviews*, 1935, **17**, 327).

In the interaction, under our conditions, of dimethyl ether with benzene and its homologues, substantial amounts of the vicinal substituted products (*o*-xylene, hemimellitene, prehnitene) are formed. In the Friedel–Crafts reaction, *o*-disubstituted products are often not found (see, *e.g.*, Ador and Rilliet, *Ber.*, 1878, **11**, 1627; 1879, **12**, 329; Moyle and Smith, *J. Org. Chem.*, 1937, **2**, 114; Shoesmith and McGechen, *J.*, 1930, 2231). Smith and Cass (*J. Amer. Chem. Soc.*, 1932, **54**, 1603, 1609) showed that in the methylation of xylene with methyl chloride in the presence of aluminium chloride, no hemimellitene or prehnitene is formed (*i.e.*, less than 1%).

The differences between the two types of reaction must be ascribed partly to differences in the equilibria, and partly to the relatively higher rates of the isomerisation reactions at the higher temperature used in the reactions of dimethyl ether.

A number of authors (see " Organic Reactions ", ed. Adams, Wiley, 1946, Price, Vol. 1*a*, p. 10) have remarked on the fact that the xylene obtained by the Friedel–Crafts reaction consists largely of the *m*-isomer; Price and Ciskowski (*J. Amer. Chem. Soc.*, 1938, **60**, 2499) have suggested that the expected *o*- and *p*-xylenes are formed first, these are methylated further to 1 : 2 : 4-trimethylbenzene, and that then a proton replaces a methyl group; substitution rules lead one to expect that *m*-xylene would be formed in this reverse reaction. This may be the mechanism by

which the *m*-isomer is formed in methylations with methyl chloride and aluminium chloride, but a similar course is impossible in the dimethyl ether gas-phase reaction, since thermodynamic data (see Part I, *loc. cit.*) show that the reactions:

$$(CH_3)_2O + C_6H_6 = C_6H_5{\cdot}CH_3 + CH_3{\cdot}OH$$
$$(CH_3)_2O + 2C_6H_6 = 2C_6H_5{\cdot}CH_3 + H_2O$$

are not reversible to any significant extent (the corresponding equilibria for the homologues will not differ greatly). In any case it is clear that the basic reason for the predominance of the *m*-isomer in both reactions is its superior stability. It is perhaps of interest to note that the compositions of coal-tar xylenes, although they vary somewhat with the source and method of preparation, are always fairly close to the equilibrium composition; certainly the *m*-isomer always predominates (Kishner and Krasova, *J. Gen. Chem. Russia*, 1936, **6**, 748, have given analyses of typical coal-tar xylenes). It is unlikely that the coal-tar xylenes, however they are produced, are formed in equilibrium proportions, or that isomerisation occurs in the gas phase, and so it appears that coal during carbonisation (presumably at temperatures of 600—1100°) catalyses the isomerisation.

The authors wish to express their thanks to the Department of Scientific and Industrial Research for a grant to one of them (P. H. G.).

DYSON PERRINS LABORATORY, OXFORD. [*Received, February 6th*, 1948.]

---

435. *Syntheses and Reactions of Mordenite.*

By R. M. BARRER.

Mordenite has been crystallised in good yield from aqueous suspensions of sodium aluminosilicate gels of compositions ranging from $Na_2O,Al_2O_3,8{\cdot}1SiO_2,nH_2O$ to $Na_2O,Al_2O_3,12{\cdot}3SiO_2,nH_2O$, the best temperature range being 265—295°; pH is as important as composition or temperature in ensuring a yield, and the best results were for a range of pH between 8 and 10 in the cold mother-liquor after crystallisation.

Simultaneously with mordenite, some analcite was obtained mainly at the silica-poor end of the composition range, and some quartz at the silica-rich end. Outside the best temperature range (265—295°) species other than these three were observed, and yields of mordenite decreased. In very alkaline solutions mordenite crystals were readily precipitated at first, but tended to redissolve and disproportionate if left too long in contact with the mother-liquor at these high temperatures.

Mordenite undergoes a ready base exchange, nitrates and chlorides giving at least partial cation replacements according to the series

$$Ca^{++} \rightleftharpoons Ba^{++} \rightleftharpoons K^+ \rightleftharpoons NH_4^+ \rightleftharpoons Na^+ \rightleftharpoons Li^+.$$

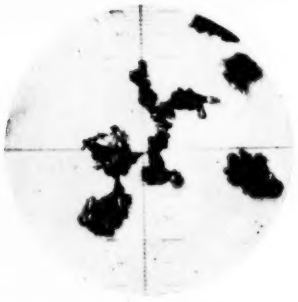
This accords with the open molecular-sieve character of the mineral, and the products when dehydrated were themselves good sorbents of gases.

It is pointed out that zeolites such as mordenite must be regarded statistically as defect structures, in which a possibly large number of new configurations introduced by base exchange give rise to a configurational entropy term. The occurrence or non-occurrence of exchanges of the types $K^+ \rightleftharpoons Na^+$, $Ca^{++} \rightleftharpoons 2Na^+$ may be influenced by the size of this entropy term relative to the corresponding energy changes.

MORDENITE, $(Na_2,Ca,K_2)O,Al_2O_3,10SiO_2,6{\cdot}7H_2O$, is one of the most highly siliceous zeolites. It is known to occur in reasonable quantity in at least one locality (private communication from Prof. A. L. Parsons, Royal Geological Museum, The University, Toronto), and has been reported in a variety of others (see Mellor, "Treatise on Inorganic and General Chemistry," Vol. VI, p. 748). With one exception (Leonard, *Econ. Geol.*, 1927, **22**, 18), its laboratory preparation has not been reported.

Recent work on its sorptive properties has shown that mordenite has a robust three-dimensional anionic network, when dehydrated is a sorbent of notable quality, and possesses, like chabazite, its own characteristic behaviour as a molecular sieve (Barrer, *Trans. Faraday Soc.*, 1944, **40**, 555; *J. Soc. Chem. Ind.*, 1945, **64**, 130). In the latter respect natural sodium-rich mordenite differs to some extent from calcium- and barium-rich mordenites prepared hydrothermally from it, although these are also excellent sorbents (*idem, ibid.*). Because of the way in which molecular-sieve sorbents can be used to separate mixtures by selective occlusion of those components small enough to permeate the dehydrated lattice, and because of the

FIG. 1.

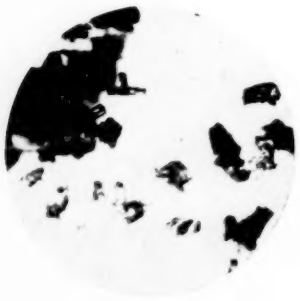


Typical clusters of synthetic mordenite crystals from gel $Na_2O,Al_2O_3,9{\cdot}4SiO_2,mH_2O$ + *aq. at* 275° *for* 4 *days. Magnified* 120 *times.*

FIG. 2.

Crystals of synthetic mordenite showing striated and wheat-sheaf appearance. Grown from gel $Na_2O,Al_2O_3,10SiO_2,mH_2O$ + *aq. by crystallising for* 2 *days at* 295°. *Magnified* 400 *times.*

FIG. 3.

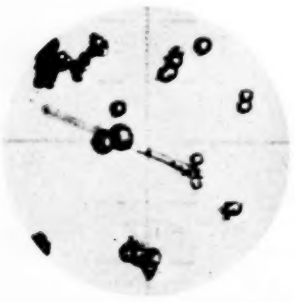


Numerous small synthetic quartz crystals grown from gel $Na_2O_2,Al_2O_3,12{\cdot}3SiO_2,mH_2O$ + *aq. at* 365° *for* 3 *days. Magnified* 120 *times.*

FIG. 4.

Quartz crystal grown for comparison purposes from silica gel with K_2CO_3 *aq. at* 360° *for* 3 *days. Magnified* 200 *times.*

FIG. 5.



Analcite spheroids, and an unidentified needle-like birefringent species grown from gel of composition $Na_2O,Al_2O_3,8{\cdot}2SiO_2,mH_2O + Na_2CO_3$ *aq. at* 216° *for* 2 *days,* i.e., *below the range of mordenite crystallisation. Magnified* 120 *times.*

FIG. 6.

Anhydrous species, grown from gel $Na_2O,Al_2O_3,8{\cdot}2SiO_2,mH_2O + Na_2CO_3$ *aq. at* 350° *for* 2 *days,* i.e., *above the range of mordenite crystallisation. Small plate-like crystals can be identified in the bottom left quadrant. The dark masses in liquids of suitable R.I. appear as clusters of elongated crystals, possibly quartz, embedded in a matrix. Magnified* 120 *times.*

[*To face p.* 2159.

interest of the zeolites as a mineral group, experiments were conducted to see whether mordenite could be made, under what conditions, and in what yields.

Experimental.

Previously analysed sodium aluminate ("Alfloc"; $NaAlO_2$, 92%, with some Na_2CO_3 and water) was dissolved in water, and the requisite volume of the opalescent solution poured into an aqueous suspension of silicic acid gel containing a trace of entrained alkali. The mixture quickly became more opaque and tended to set. It was variously evaporated to dryness or to a thick consistency at temperatures not above 110° and sometimes as low as 70—80°.* If dried, the product was powdered before being stored for use. Aluminosilicate gels were prepared of the compositions: $Na_2O,Al_2O_3,8{\cdot}2SiO_2,nH_2O$; $Na_2O,Al_2O_3,9{\cdot}36SiO_2,nH_2O$; $Na_2O,Al_2O_3,10{\cdot}0SiO_2,nH_2O$; $Na_2O,Al_2O_3,10{\cdot}9SiO_2,nH_2O$; $Na_2O,Al_2O_3,12{\cdot}3SiO_2,nH_2O$. Gels of exact mordenite composition were dried in several ways to determine whether the conditions of preparation were related to yield (p. 2162); and also many gels poorer in silica were prepared, which, however, proved unsuitable for making mordenite although often giving high yields of other crystalline aluminosilicates.†

Portions of the gel, usually of several g., were then introduced with 10—15 c.c. of water into stainless-steel autoclaves of approximately 25 c.c. capacity. The autoclaves were sealed by a screw-top bearing on a soft-copper washer, which flowed slightly under pressure to give a vacuum-tight seal. The autoclaves were then placed in an air-thermostat operating up to 300°. Alternatively, especially for experiments above 300°, nichrome-wound furnaces, manually controlled, were used.

The products were examined under the polarisation microscope, and were investigated as sorbents (Barrer, in the press). Sorption was occasionally employed to estimate the yield of mordenite, once the presence of that mineral was revealed, since the ratio of the saturation sorption in a synthetic mineral and a natural mordenite for a given gas at a given temperature (oxygen at $-$ 185°) gives the percentage purity.‡ For the final proof of the identity of synthetic and natural mordenites, *X*-ray powder photographs were used.

Pure or A.R. salts were employed in experiments on base-exchange reactions of mordenite. In order to promote completeness of reaction, an excess of the exchanging salt was used. This was ground with powdered mordenites before addition of 10—15 c.c. of water and heating above 200°. Since the products were required intact for sorptive studies, progress of base exchange was for the most part followed by determining the displaced calcium in the mother-liquor rather than by destruction of the solid in analysis. These base-exchange products were as far as possible freed from entrained salt by washing with water at 100°, and then further extracted with water above 200° to ensure that no more removable salt remained.

Results.—A number of experiments established that crystallisation readily occurred to give mordenite as one of the species, and that best yields were obtained in the range 265—295°. The mordenite was obtained, as indicated in Figs. 1 and 2, in the form of matrices of elongated crystallites, and as wide, flat crystals with a fibrous or striated appearance. They were feebly birefringent and had a mean refractive index of 1·464—1·472. The extinction was nearly parallel (0°$\pm$15°), but the small size of the crystals made their further optical characterisation difficult.§ The crystals were further established as mordenitic by their sorptive and molecular sieve behaviour (Barrer, *loc. cit.*, 1944; in the press) and by a detailed comparison of transient states of flow of gases in them in natural mordenites, and in the base-exchange mordenites prepared in this work. *X*-Ray powder photographs of synthetic, natural, and base-exchange mordenites gave the spacings in Table I. There is excellent agreement between the sequence of intensities of the lines as well as in the actual spacings for natural mordenite, the synthetic sodium mordenite, and sodium mordenite prepared by base exchange. The correspondence extends within experimental error over as many lines as could be observed. Moreover, all the base-exchange products enriched in Na, K, Li, NH_4, Ca, or Ba give diffraction patterns clearly characteristic of mordenites, showing that exchange can occur without recrystallisation under the conditions described in Table III.

At the gel compositions referred to above mordenite was the dominant species, very high yields often being obtained. Other species could also be grown from the same gels, however, which included quartz (Fig. 3) and analcite (Fig. 5). These were identified by comparison with synthetic analcites (see footnote ‡ below, and Barrer, this vol., p. 127) and quartz (Barrer, *Nature*, 1946, **157**, 734) previously prepared. Not all the crystals grown under various conditions from the gels could be identified (*e.g.*, Figs. 5 and 6).

Brief details of the experiments given in Table II provide a clearer idea of the best conditions for preparing mordenite. Especially interesting are experiments *e*, *f*, and *g* in Section (iii) of the table. A creamy aluminosilicate gel of mordenite composition, which yielded a very alkaline mother-liquor both before and after crystallisation, gave little recognisable mordenite after *two* days at a high pH,

* Drying at high temperatures tends to insolubilise the aluminosilicate gel, and to lead to poor crystallisation under hydrothermal conditions.

† The species produced from silica-poor aluminosilicate gels were diverse, and will be discussed in later communications.

‡ Analcite was also present in many preparations, but pure synthetic analcites have not been found to occlude oxygen.

§ The mean refractive index of natural mordenite may be taken as about 1·475 $\pm$ 0·005, but whereas the synthetic mineral contained only Na as cations, natural mordenites normally contain several cations (Na, Ca, K). The extinction angle of mordenite has been reported as about 15°, while that of the closely allied zeolite, ptilolite, has been given as 0° (Mellor, *op. cit.*, Vol. VI, p. 748). Ptilolite may even be identical with mordenite (Walker and Parsons, *Univ. Toronto Geol. Studies*, 1922, **14**, 13; but see Schaller, *Amer. Min.*, 1923, **8**, 93, 169).

TABLE I.

Spacings in A. *of natural, synthetic, and base-exchange mordenites using* Cu-$K\alpha$ 40 *kv.* X-*rays.*

Natural mordenite.	Synthetic sodium mordenite.	Base-exchange mordenites.					
		Na.	K.	NH_4.	Li.	Ca.	Ba.
13·5 s	13·4 ms	13·5 m	13·5 ms	13·6 w	13·6 m	13·7 m	—
8·66 s	8·85 ms	8·95 s	9·02 vs	8·90 ms	8·88 s	8·90 s	9·0 s
6·54 s	6·49 ms	6·52 ms	6·65 vvw	6·59 m	6·69 m	6·65 s	6·44 s
5·72 m	5·66 mw	5·66 w	—	5·88 vw	—	5·83 mw	5·78 m
—	—	—	5·37 vw	5·27 vvw	5·14 w	—	—
—	—	—	—	—	—	—	4·81 w
4·50 s	4·50 ms	4·52 s	4·66 w	4·57 m	4·56 ms	4·55 ms	4·49 s
3·99 s	3·98 vs	3·98 vs	4·08 vs	4·02 s	3·98 vs	3·99 s	3·97 vs
—	—	—	3·77 w	—	—	—	3·76 w
3·40 s	3·42 vs	3·42 vs	3·48 m	3·40 s	3·43 vs	3·48 vs	3·43 vs
3·15 s	3·15 s	3·16 vs	3·21 ms	3·16 ms	3·19 s	3·17 s	3·21 s
2·90 ms	2·89 ms	2·83 m	2·99 vs	2·92 vw	2·91 s	2·88 m	2·89 ms
2·70 vw	2·67 vw	—	2·80 m	2·69 vw	2·73 ms	2·70 vw	2·70 vw
2·50 m	2·52 m	2·48 mw	2·53 w	2·50 vw	2·50 ms	2·54 mw	2·51 ms
2·43 w	2·45 vw	2·43 w	2·45 vw	2·42 vw	2·41 w	2·42 vvw	2·46 w
—	—	—	—	—	—	—	2·27 vw
2·02 mw	2·01 w	2·01 w	2·04 w	2·03 vw	2·04 mw	2·03 w	2·12 vvw
1·94 mw	1·94 w	1·96 w	—	1·94 w	1·95 mw	1·95 vw	1·95 w
$1·85_5$ mw	$1·86_2$ w	$1·86_5$ w	$1·85_4$ vvw	$1·86_3$ vw	$1·86_6$ w	$1·88_0$ w	$1·87_5$ mw
$1·78_5$ mw	$1·79_2$ w	$1·79_7$ mw	$1·80_9$ m	$1·75_5$ vvw	$1·80_5$ w	$1·79_7$ w	$1·79_2$ mw
$1·68_7$ vvw	$1·70_4$ vw	$1·69_0$ vvw	$1·67_0$ vvw	$1·68_4$ vw	—	$1·68_8$ w	$1·66_3$ vw
$1·64_6$ vvw	$1·65_8$ vvw	—	—	$1·64_8$ vw	—	—	—
$1·58_5$ vw	$1·59_0$ vw	$1·61_5$ mw	$1·62_8$ vvw	$1·59_6$ vvw	$1·60_5$ vw	—	$1·60_1$ vvw
$1·52_7$ w	$1·52_8$ w	$1·52_9$ w	$1·55_9$ w	$1·52_6$ vvw	$1·53_4$ vw	—	$1·53_9$ mw
$1·47_7$ w	$1·47_5$ vw	$1·47_9$ vvw	$1·49_0$ vw	$1·47_6$ vvw	$1·48_6$ vw	$1·49_2$ vvw	$1·47_9$ vw
$1·43_9$ m	$1·44_3$ mw	$1·44_2$ mw	$1·45_5$ vw	$1·44_1$ vvw	$1·44_5$ vw	$1·44_9$ w	$1·44_0$ mw
$1·41_5$ vvw	$1·40_8$ vw	$1·40_5$ w	—	$1·40_0$ vvw	$1·40_8$ vw	—	$1·40_7$ vw
$1·37_6$ vvw	$1·37_5$ w	—	—	$1·37_2$ vvw	$1·37_6$ vvw	$1·37_5$ vw	$1·37_7$ mw
$1·35_0$ vw	$1·34_9$ vw	$1·34_6$ w	$1·35_8$ vw	$1·34_8$ vvw	$1·35_2$ vvw	—	$1·35_4$ vvw
$1·31_1$ vvw	—	—	—	—	—	—	—
$1·29_1$ vw	$1·29_5$ vw	$1·29_1$ vw	$1·30_2$ vw	$1·31_4$ vvw	$1·29_6$ vvw	$1·29_5$ vvw	$1·29_6$ vvw
$1·26_2$ vw	$1·26_2$ vw	$1·26_1$ vvw	$1·27_6$vvw	$1·25_9$ vvw	$1·27_2$ vvw	$1·26_4$ vvw	$1·25_8$ vvw
$1·23_8$ vw	$1·23_9$ vvw	$1·24_1$ vvw	$1·24_2$ vw	$1·23_8$ vvw	$1·24_6$ vvw	$1·24_1$ vvw	$1·24_2$ vvw
$1·21_1$ vvw	$1·21_9$ vvw	—	—	—	$1·22_2$ vvw	$1·21_9$ vvw	$1·21_1$ vvw
$1·18_9$ vvw	$1·17_4$ vvw	—	$1·16_5$ vw	—	$1·17_6$ vvw	$1·18_1$ vvw	—
$1·15_4$ vvw	$1·15_7$ vvw	—	—	—	—	—	—
$1·12_5$ vvw	$1·12_4$ vvw	—	—	—	—	$1·12_1$ vvw	—
$1·09_5$ vvw	—	—	—	—	—	—	—

Col. 1 : Mineral supplied by Dr. A. L. Parsons.
Col. 2 : Product of Table II, Section (iii), Expt. *a*.
Col. 3 : From mordenite using saturated NaCl solution, two treatments each of one day at 220°, followed by H_2O extraction at 220°.
Col. 4 : Products Nos. 7 and 8 of Table III used.
Col. 5 : From mordenite using NH_4Cl vapour, two treatments each of one dav at 300°, followed by hydrothermal extraction at 220°.
Col. 6 : Product No. 6 of Table III used.
Col. 7 : Product No. 9 of Table III used.
Col. 8 : Product No. 11 of Table III used.

but gave good yields when the reaction time was shortened to *one* day or less. Moreover, the mordenite crystals which were observed in the two-day experiment seemed considerably corroded. It is probable, therefore, that at ~280° mordenite is unstable over a period in very alkaline media, and, perhaps owing to its high silica content, disproportionates into other products, such as analcite, poorer in silica, and possibly sodium silicates poorer in alumina, which, however, were not observed to crystallise from the mother-liquor. Since an alkaline medium at 280° *initially* favours crystallisation as mordenite (experiments *f* and *g*), this would appear to be an example of primary precipitation of a thermodynamically less stable species followed by its subsequent conversion into other species at a rate depending upon the alkalinity.

Although too high a pH accelerates the decomposition of mordenite, none the less a considerable measure of alkalinity is needed for good crystal growth in the gel. At too low pH, probably owing to a smaller solubility of the gel in such conditions, the crystallisation became retarded and the crystals fewer and smaller.* This is in good agreement with the assumption that zeolite formation is favoured by an alkaline reaction medium (Lindgren, "Mineral Deposits," McGraw Hill Book Co., 1919, p. 427).

* In Table II, Section (v), Expt. *j*, a gel $Na_2O,Al_2O_3,8·2SiO_2$ was heated with boric acid solution at ~275°. No mordenite could be detected, and only a few crystals of any kind, the pH after reaction being 7—7·5.

TABLE II.

Hydrothermal crystallisation of aluminosilicate gels, $Na_2O,Al_2O_3,mSiO_2,nH_2O$.

Section and Expt.	Condition of crystallisation.	pH of cold mother-liquor after reaction.	Products and yields.
	Composition of gel: $Na_2O,Al_2O_3,12{\cdot}3SiO_2 + H_2O$.		
(i) *a*	~265° for 3 days	10—10·5	Quartz, analcite, some mordenite, and very fine needles
b	~365° for 3 days with aq. $NaHCO_3$	9·5—10	Fine quartz crystals. Large yield of unidentified species
	Composition of gel: $Na_2O,Al_2O_3,10{\cdot}9SiO_2 + H_2O$.		
(ii) *a*	~290° for 2 days	—	Mordenite. Little analcite and rare quartz
b	~295° for 3 days with aq. $NaHCO_3$	—	Mordenite with a little quartz
	Composition of gel: $Na_2O,Al_2O_3,10SiO_2 + H_2O$.		
(iii) *a*	~295° for 2 days	~10·0	Good yield of mordenite and a little analcite
b	~290° for 2 days	9·5—10	Mordenite. Some analcite
c	~295° for 2 days	~9·0	Excellent yield of mordenite. Some analcite
d	~295° for 2 days	~7·5(?)	Mordenite, some analcite. Not well crystallised
e	~280° for 2 days	10—10·5	Rare mordenite, with crystals rather corroded. Some analcite
f	~290° for 1 day	~10·5	Good yield of mordenite and some analcite
g	~280° for 17 hrs.	—	Good yield of mordenite
	Composition of gel: $Na_2O,Al_2O_3,9{\cdot}3SiO_2 + H_2O$.		
(iv) *a*	~290° for 3 days	—	Considerable analcite and mordenite. A little quartz and some masses of needle-shaped crystals
b	~275° with $NaHCO_3$ solution for 2 day	—	Some mordenite and analcite
c	~275° for 4 days	—	Good yield of mordenite, with some analcite. Moisture content of crystals 12·5%
	Composition of gel: $Na_2O,Al_2O_3,8{\cdot}2SiO_2 + H_2O$.		
(v) *a*	~210° with aqueous 2N-$CaCl_2$ for 36 hrs.	8—8·5	Little obvious crystallisation
b	~290° for 36 hrs.	8—8·5	Analcite and mordenite in considerable yield
c	~350° for 2 days	—	Quartz, indeterminate masses, and rare small needle-like crystals
d	~216° with 2N-Na_2CO_3 solution for 2 days	~10·0	Mainly analcite, with rare, long, dagger-shaped or ribbon-like crystals of n 1·490, often showing twinning
e	~350° with 2N-Na_2CO_3 solution for 2 days	~10·0	Some 8- or 6-sided plates of n 1·52, often twinned. Clusters of acicular crystals in a matrix. No water of crystn.
f	~290° with 2N-Na_2CO_3 solution for 1 day	~10·0	Much analcite and mordenite, and a little quartz
		~8·0	Excellent yield of mordenite
h	~290° for 36 hrs. with borate buffer of initial pH 7·6	~8·5	Fair yield of analcite and mordenite
i	~295° for 2 days with $NaHCO_3$ solution	~9	Mainly analcite. Some quartz and mordenite
j	~275° for 2 days with considerable H_3BO_3	7—7·5	Small amount of analcite. Rest indeterminate

In syntheses of harmotone, analcite, and several synthetic zeolites, the author has not found any exceptions to this rule.* At temperatures of 280—290° mordenite was observed when the pH of the cold mother-liquor after crystallisation lay between 7·5 and 10·5; pH's above 10·5 were not studied, and consistently good yields were observed at pH's of 8 to 10. It is believed that pH can be as important a variable in hydrothermal reactions as temperature or composition.

Table II also shows the great influence of temperature on the nature of the species (*e.g.*, Section v). Successful syntheses refer mainly to temperatures of 265—295°. On the other hand, in the ranges 210—220° and 350—370° mordenite was superseded by other species, so that the 265—295° range is most appropriate for syntheses of this mineral. This temperature range is well above that at which analcite first appeared (~180—220°), and the range of its hydrothermal occurrence is much less (analcite was still moderately abundant at 300—310° when suitable gels were crystallised). Table II also records attempts to trace the influence of varying the thermal histories of the gels upon the yield of mordenite

* Syntheses of these and other aluminosilicates will be discussed elsewhere.

(Section iii). In all experiments a gel was first made by the usual mixing of sodium aluminate solution with silicic acid gel in suspension. The creamy gel was used with no further treatment in (iii) *e*, *f*, and *g*; but the products used in (iii) *a*, *b*, *c*, and *d* were obtained as follows

Creamy gel

(*a*).	(*b*).	(*c*).	(*d*).
Stood for 48 hrs. and evaporated to dryness over a water-bath.	Evaporated at once fairly quickly in air-oven at 110°.	Stood for 16 hrs. and evaporated to dryness on a water-bath.	Evaporated at once to dryness on a water-bath.

Good yields were obtained from all the samples, whatever the thermal history within the above range of treatments. All the other gels in Table II were prepared under conditions falling within this range, and therefore their preparation need not be individually described.

Finally, it should be noted that considerable variations in the composition of the crystallising gel are possible, and that at the silica-richer end of this range quartz often appears in some quantity. At the silica-poor end of the range analcite ($NaAlSi_2O_6.H_2O$) is found in increasing quantity. It is thus better to keep to the mordenite composition in the parent gel.

Base-exchange Reactions of Mordenite.—The base-exchange reactions of mordenite appear to have been little studied (Barrer, *loc. cit.*, 1944), but since the sorptive and molecular-sieve properties show the mineral to have an open anionic network structure, base exchange should occur readily. A series of hydrothermal treatments using nitrates and chlorides in excess (3—5 g.), several g. of powdered mordenite, and 10—15 c.c. of water showed that this was indeed the case (Table III). One sample of the natural mordenite used was found to contain:

	% on dry weight.	Molar proportion.		% on dry weight.	Molar proportion.
SiO_2	78·5	9·44	CaO	3·5	0·45
Al_2O_3	14·1	1·00	Na_2O (by diff.)	4·1	0·48 (as Na_2O)

Although this analysis may be taken as typical, the ratio of alkali- to alkaline-earth metal may have varied among the different samples used for base exchange.

After any experiment the base-exchanged product was washed thoroughly with distilled water at ~100°, until the washings were free from salt, and then treated several times with distilled water between 220° and 250° in an autoclave to ensure that all removable salt was extracted. The samples were then submitted to *X*-ray examination, and to investigation as sorbents and molecular sieves (Table III). Specimens of Ca, Ba, K, NH_4, Li, and Na mordenites afforded Debye–Scherrer photographs typical of mordenite (Table I). Similarly, Ca, Ba, K, Li, NH_4, and Na mordenite used as sorbents were found to have good sorbent and molecular-sieve properties although modified slightly from those of mordenite in characteristic ways (Barrer, in the press). The extraction process, sorptive properties, and *X*-ray data make it clear that the interstitial channels are not blocked by occluded salt. Analysis and tests either of calcium or of sodium displaced into the mother-liquor, or of the solid, showed moreover that the lattice had been much enriched in the exchanging cation.

Solids submitted to analysis were those of Table III, Expt. 9, where the CaO content corresponded to 0·88 mol. of CaO per mol. of Al_2O_3, and of Table III, Expt. 6, where some 15% of the total alkali had been replaced by Li_2O, a rather less complete exchange than might have been expected from Table III, Expt. 2.

Taken as a whole, data of Table III show that exchanges can involve a wide variety of cations expressible by the series

$$Ca^{++} \rightleftharpoons Ba^{++} \rightleftharpoons K^+ \rightleftharpoons NH_4^+ \rightleftharpoons Na^+ \rightleftharpoons Li^+$$

The diameters of the interstitial channels in natural mordenite are just a little above 4·0 A. at their narrowest point (Barrer, *loc. cit.*, 1944), while the ionic diameters of the exchanging cations and their associated anions are:

Ion.	Li^+.	Na^+.	K^+.	NH_4^+.	Ca^{++}.	Ba^{++}.	Cl^-.	NO_3^-.
Diameter (in A.)	1·20	1·90	2·66	2·86	1·98	2·70	3·62	5·1

Thus the cations alone should, as observed, diffuse readily in the lattice. The chloride ion might just enter, but the nitrate ion could not unless the lattice recrystallised. It was these diameters which guided the choice of chlorides and nitrates respectively, as exchangers. In fact, neither anion as a rule showed any tendency to be occluded.

Base exchanges represented in the above cations series can be of two kinds typified by $K^+ \rightleftharpoons Na^+$ and $Ca^{++} \rightleftharpoons 2Na^+$. On the assumption that the univalent cations occupy all possible sites, it is a matter for speculation as to which of the sites are occupied by only half the number of bivalent cations. In many zeolites it is true that both uni- and bi-valent cations occur interstitially (*e.g.*, mordenite, chabazite, and gmelinite) so that random cation distributions, leaving many vacant sites, may arise. In this sense these zeolites are to be regarded as defect structures. The entropy of such crystals may be substantially above that of normal crystals, where only one cation configuration is possible. If there are N cation sites, N^+ univalent cations, and N^{++} bivalent cations, the distinguishable configuration number $\frac{N!}{N^+!N^{++}!(N-N^+-N^{++})!}$, and, Stirling's approximations being used, the configurational entropy S_c due to this becomes

$$S_c = k[N \ln N - N^+ \ln N^+ - N^{++} \ln N^{++} - (N - N^+ - N^{++}) \ln (N - N^+ - N^{++})] \quad . \quad (1)$$

TABLE III.

Typical base-exchange reactions of mordenite.

Expt. no.	Salt.	Reaction conditions.	Analysis of mother-liquor or solid.	Observations.
1	NaCl	Two successive hydrothermal treatments at 200° and 230°, of 2 and 7 days respectively	Considerable Ca displaced from mordenite into mother-liquor. Qualitative test only	Excellent mordenite *X*-ray powder photograph. Birefringent
2	LiCl	Two successive treatments as above at 220°, each of ~1 day	First treatment displaced 1·61% CaO; 2nd displaced 0·29% CaO (by wt.)	Molecular sieve sorbent. Birefringent
3	NH_4Cl	Two successive treatments with NH_4Cl vapour at 250° and 290°, each of 2 days	1·66% CaO displaced in 1st treatment and 0·15% in 2nd (by wt.)	Molecular sieve sorbent. Birefringent
4	$CaCl_2$	Two successive treatments at 200°, each of ~3 days	Solid free from incorporated Cl	Good mordenite *X*-ray powder photograph. Birefringent
5	$NaNO_3$	Two successive treatments at 222°, each of nearly 1 day	First treatment displaced 1·41% CaO, 2nd displaced 0·31% CaO (by wt.)	Birefringent
6	$LiNO_3$	Two successive treatments at 250° of 2 days and 1 day respectively	Analysis of alkali and alkaline-earth metals in solid showed 15% replacement by Li	Birefringent. *X*-Ray photograph similar to that of mordenite. Molecular sieve solvent
7	KNO_3	Two successive treatments at 222°, each of 1 day	First treatment displaced 1·62% CaO; 2nd displaced 0·37% CaO (by wt.)	Sorbent of molecular-sieve type. *X*-Ray pattern similar to that of mordenite. Birefringent
8	KNO_3	Two successive treatments at 200°, each of 3 days	—	*X*-Ray pattern similar to that of mordenite. Birefringent
9	$Ca(NO_3)_2$	Three successive treatments at 225°, each 1 day	Solid analysed: 88% of total alkali was now CaO	Molecular sieve sorbent. Birefringent
10	$Ca(NO_3)_2$	Two successive treatments at 265°, of 2 and 3 days respectively	Considerable Na displaced from mordenite in 1st treatment (tested by zinc uranyl acetate)	Good sorbent as above. *X*-Ray pattern similar to that of mordenite. Birefringent
11	$Ba(NO_3)_2$	Three successive treatments at 260°; 3½, 2½, and 1½ days respectively.	Much Na displaced from mordenite in first treatment. Little Na displaced in last two	Molecular sieve sorbent. *X*-Ray pattern similar to that of mordenite. Birefringent

If all the bivalent cations are replaced by an electrochemical equivalent of univalent cations, and if the total number of univalent cations is equal to the number of sites, substitution in (1) gives $S^{+}_{e} = 0$. If, however, the bivalent cations replace all the univalent ones, one has $N^{+} = 0$, $N^{++} = \frac{1}{2}N$, and so

$$S_e^{++} = Nk \ln 2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

i.e., there is an increase in entropy during replacement of univalent by bivalent cations. There is at the same time likely to be a change in internal energy, because there is a change in the local neutralisation of anionic charge in the crystal on the smallest possible scale and also because of a changed bonding energy of interstitial water molecules associated with the cations. Now the net free-energy change for replacement is:

$$\Delta G^{++} = \Delta H^{++} - T\Delta S^{++} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and whether replacement of uni- by bi-valent cations will occur or not depends on the relative sizes and signs of the two terms on the right-hand side of (3). For example, if each is of the same order of magnitude, and the same sign, one may have exchange going in either direction (chabazite, mordenite, gmelinite); if ΔH^{++} is larger than $T\Delta S^{++}$, replacement of uni- by bi-valent cations will be limited (analcite); and if $\Delta H^{++} < T\Delta S^{++}$, bivalent cations will be little replaced by univalent ones. At the temperature of the exchange reactions in this paper $T\Delta S_e^{++}$ is likely to contribute not more than 800 cals./g.-ion to the over-all value of ΔG.*

I am glad to acknowledge a grant from The Royal Society towards the cost of this work, and a grant from Imperial Chemical Industries Ltd. for the purchase of *X*-ray equipment on loan.

BEDFORD COLLEGE (UNIVERSITY OF LONDON),
REGENT'S PARK, N.W.1.

[*Received, February 13th,* 1948.]

* ΔS_e^{++} is, however, only part of the over-all entropy, ΔS, of exchange.

436. *Colour Reactions and Adsorption of Some Aluminosilicates.*

By H. Weil-Malherbe and J. Weiss.

It is known that a number of substances such as aromatic amines and vitamin-A produce deep colours on certain aluminosilicate minerals. These phenomena have been investigated and it has been found that two different mechanisms are responsible for this.

Reactions similar to that of vitamin-A can be produced with other molecules possessing a system of conjugated double bonds, and these colour reactions are observed only if the aluminosilicate possesses the functions of an acid. It is thus closely related to the phenomenon of "halochromy" and is due to the formation of salt-like surface compounds, the conjugated system acting as base. In the case of benzidine and related substances the colours produced are due to the oxidative formation of radicals by certain metal ions of the crystal lattice (*e.g.*, Fe^{3+}). The corresponding adsorption isotherms have been investigated in some detail. The significance of these reactions for the catalytic action of aluminosilicates is discussed.

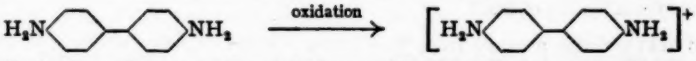
In recent years a number of colour reactions attendant upon the adsorption of various substances on aluminosilicate minerals have been described, particularly those produced by benzidine and other aromatic amines (Hauser and Leggett, *J. Amer. Chem. Soc.*, 1940, **62**, 1811; Krüger and Oberlies, *Ber.*, 1941, **74**, 1711; *Naturwiss.*, 1943, **31**, 92) and those produced by vitamin-A and other carotenoids (cf. Meunier, *Bull. Soc. chim.*, 1946, **13**, 73, 77). However, no clear distinction between these various groups of colour reactions has been made, and little is known about the mechanism of colour formation. We have investigated the ability of some silicate minerals to produce coloured adsorption compounds and, as a result, a classification of these phenomena now seems possible. In addition, the adsorption isotherms of colour-producing and non-colour-producing systems were studied.

Aluminosilicates which occur in Nature as various clays are of great importance as catalysts, *e.g.*, in the isomerisation and cracking of hydrocarbons. Since our results contribute to the understanding of the chemical reactivity of these compounds, they may also have some bearing on their catalytic action.

(1) *Colour Reactions.*—Our results indicate that there are two mechanisms underlying colour formation:

(i, *a*) In the first group, colour formation is presumably due to an acid–base type of reaction. Substances which are known to give deep colours with strong acids such as concentrated sulphuric acid (cf. Hammett, "Organic Chemistry," McGraw-Hill, 1941) also produce identical or very similar colours upon adsorption on suitable clays. A number of these halochromic substances owe their electron-donating, *i.e.*, basic, properties to a system of conjugated double bonds, *e.g.*, dicinnamylideneacetone, dianisylideneacetone, and similar ketones, and vitamin-A and other carotenoids. Their basic character is, however, so weak that the coloured salts are easily hydrolysed by water. Others, like dimethylaminoazobenzene and other azo-dyes, are stronger bases and are able to form coloured ions even in an aqueous medium. The two classes of compound show an analogous behaviour towards adsorbing clays. As shown in Table I the clays react like acids, and this can be modified by suitable treatments. Pre-treatment with hydrochloric acid usually enhances the intensity of the colour reactions; on the other hand, dicinnamylideneacetone and vitamin-A, which are very weak bases, are no longer chromogenic on ammonia-treated clays. Owing to their stronger basicity, azo-dyes still show the colour of their ions, though with reduced intensity, on clays after ammonia-treatment. The inhibition of the colour reactions by ammonia treatment is reversible by acid treatment and *vice versa*.

(i, *b*) The colour production in the second group is presumably due to an oxidation–reduction mechanism. An example is the colour reaction of benzidine (Hendricks and Alexander, *J. Amer. Soc. Agron.*, 1940, **32**, 455; Endel, Zorn, and Hofmann, *Angew. Chem.*, 1941, **54**, 376) and of other aromatic amines studied more recently by Krüger and Oberlies (*loc. cit.*) and by Hauser and Leggett (*loc. cit.*). The benzidine-blue reaction is known to be due to the oxidation of benzidine to the univalent benzidine cation (cf. Weiss, *Chem. and Ind.*, 1938, **57**, 517):



We found that the colour reaction of clays with benzidine remained unaffected by pre-treatment of the clays with acids or bases, but it was generally suppressed after the clays had been refluxed with a solution of 10% stannous chloride in concentrated hydrochloric acid. The colour reactions given by the halochromic substances of group (i, *a*) are unaffected by this treatment.

TABLE I.

*Colour reactions on aluminosilicate clays.**

Substrates dissolved in benzene (approx. 0·01 mg. per cent. solutions).

Adsorbent.	Benzidine.	Dicinnamylidene-acetone.	Vitamin-A.	Azo-dyes.
A. Untreated clays.				
Clarit	+	+	+	+
Fuller's earth	+	+	+	+
Bentonite	+	−	−	(+)
Montmorillonite	(+)	+	+	+
Kaolin	(+)	+	+	+
B. After hydrochloric acid treatment.				
Clarit	+	+	+	+
Fuller's earth	+	+	+	+
Bentonite	+	+	+	+
Montmorillonite	(+)	+	+	+
Kaolin	(+)	+	+	+
C. After ammonia treatment.				
Clarit	+	−	−	(+)
Fuller's earth	+	−	−	(+)
Bentonite	+	−	−	(+)
Montmorillonite	(+)	−	−	(+)
Kaolin	(+)	−	−	(+)
D. After stannous chloride treatment.				
Clarit	−	+	+	+
Fuller's earth	−	+	+	+
Bentonite	(+)	+	+	+
Montmorillonite	−	+	+	+
Kaolin	−	+	+	+

* + positive, (+) weakly positive, − negative.

Our specimens of montmorillonite and kaolin gave only a feeble benzidine reaction, which appeared after several minutes and slowly increased in intensity. This slow development of colour was in marked contrast to the instantaneous reactions observed in group (i, *a*) and in itself suggests a different reaction mechanism. Stannous chloride treatment completely suppressed the benzidine reaction of these two clays, as also of fuller's earth and clarit; with bentonite only a partial inhibition was obtained. Refluxing with concentrated hydrochloric acid alone or treatment with sodium sulphide and oxalic acid (cf. Dion, *Soil Sci.*, 1944, **58**, 711), which is supposed to remove the loosely bound intermicellar iron, had no effect. This suggests that the colour formation, influenced by stannous chloride treatment, is related to lattice-bound oxidising ions, most probably ferric ions, and the assumption is further supported by the analysis of fuller's earth and clarit before and after stannous chloride treatment, showing a decrease of iron content (Table II). It is possible that the remaining iron has been reduced to the inactive ferrous form by stannous chloride.

Heating with concentrated hydrochloric acid in a sealed tube at 150° completely destroyed both the colour-producing properties and the adsorption capacity of all clays. *X*-Ray analysis of the minerals thus treated showed that their natural structure had disappeared. Colour formation and adsorption therefore depend on the crystallographic structure.

TABLE II.

Iron content of clays before and after stannous chloride treatment.

Substance.	Treatment.	Fe, %.	Benzidine reaction.
Clarit	HCl-treated (refluxed)	1·54	+
	$SnCl_2$-treated	0·42	−
Fuller's earth	HCl-treated (refluxed)	1·13	+
	$SnCl_2$-treated	0·73	−

(2) *Adsorption Properties.*—Since both colour production and adsorption are surface phenomena, their mutual relationship was investigated by determining the adsorption isotherms of systems consisting of a chromogenic substance and an adsorbent clay which was either in a state in which it gave a positive colour reaction or in which the colour production had been

prevented by a suitable treatment. In practically every case the adsorption could be represented by the Freundlich isotherm $q = \alpha c^n$, where at equilibrium, q = millimols. of solute adsorbed per g. of adsorbent, c = concentration of the solute in the supernatant solution (mol./l), and α and n are constants. The value of n in the above equation was determined graphically from the log q–log c curve; the constancy of the values for α provides a test for

TABLE III.

Adsorption isotherms calculated according to the equation $q = \alpha c^n$.

Adsorbent.	Substrate.	Adsorbent, mg.	$10^3 q$.	$10^3 c$.	n.	α
Bentonite, HCl-treated	Benzidine	7·6	252·3	0·0532	0·101	0·680
		33·2	219·6	0·0158		0·669
		90·4	263·9	0·0956		0·670
		179·9	343·8	1·263		0·673
Fuller's earth (Redhill), $SnCl_2$-treated	Benzidine	13·5	117·1	0·232	0·350	2·196
		38·9	147·2	0·452		2·187
		94·9	200·9	1·119		2·173
		177·6	293·3	3·161		2·205
Bentonite, $SnCl_2$-treated	AAT *	9·7	96·2	0·258	0·078	0·183
		39·8	100·5	0·555		0·180
		131·0	110·4	1·755		0·181
		148·0	128·2	10·51		0·183
Bentonite, HCl-treated	DCA †	10·1	59·2	0·230	0·131	0·177
		34·7	60·4	0·629		0·159
		76·0	79·1	2·293		0·175
		147·0	89·9	7·842		0·170

* AAT = 4-Amino-2′ : 3-azotoluene.
† DCA = Dicinnamylideneacetone.

TABLE IV.

*Constants of the Freundlich adsorption isotherm, and colour formation of some clay minerals.**

Determination.	AAT.	DCA.	Benzidine.
Bentonite, untreated.			
Colour	(+)		
α	1·47		
n	0·94		
Bentonite, HCl-treated.			
Colour		+	+
α		0·170	0·67
n		0·13	0·101
Bentonite, NH_3-treated.			
Colour	(+)	−	+
α	0·196	1·42	1·71
n	0·72	0·668	0·33
Bentonite, $SnCl_2$-treated.			
Colour	+		
α	0·182		
n	0·078		
Fuller's earth (a), untreated.			
Colour	+		
α	0·98		
n	0·42		
Fuller's earth (a), HCl-treated.			
Colour		+	+
α		1·56	0·90
n		0·426	0·13
Fuller's earth (a), HCl-refluxed.			
Colour			+
α			1·33
n			0·218

Determination.	AAT.	DCA.	Benzidine.
Fuller's earth (a), NH_3-treated.			
Colour	(+)	−	+
α	0·073	3·60	2·70
n	0·25	0·89	0·39
Fuller's earth (a), $SnCl_2$-treated.			
Colour	+		−
α	2·00		2·20
n	0·64		0·35
Fuller's earth (b), HCl-treated.			
Colour			+
α			0·50
n			0·062
Fuller's earth (b), NH_3-treated.			
Colour			+
α			0·20
n			0·169
Clarit, HCl-refluxed.			
Colour			+
α			1·50
n			0·21
Clarit, $SnCl_2$-treated.			
Colour			−
α			5·63
n			0·51
Montmorillonite, HCl-treated.			
Colour			(+)
α			1·59
n			0·25

* Fuller's earth: (a) from Redhill, Surrey; (b) supplied by British Drug Houses Ltd.

the validity of the adsorption isotherm. The deviations from the mean value of α were small throughout. Space does not permit the full communication of our results but a few typical examples are reproduced in Table III. In Table IV values of α and n for various adsorbents have been correlated with the colour formation.

The adsorption experiments show that adsorption may be relatively strong even when the colour reaction is negative. It is clear, however, from the figures of Table IV that the character of the adsorption isotherm does not remain unaltered by a treatment which destroys the colour reaction. There seems to be a general tendency for both the constants α and n to assume low values if the adsorbent is or becomes strongly colour-positive. In order to understand the significance of these changes it is necessary to consider a theoretical interpretation of the Freundlich isotherm. Such treatments have been given by Henry (*Phil. Mag.*, 1922, **44**, 689) and Zeldovitch (*Acta Physicochim. U.S.S.R.*, 1934, **1**, 961). More recently Cremer and Flügge (*Z. physikal. Chem.*, 1938, *B*, **41**, 453) and Halsey and Taylor (*J. Chem. Physics*, 1947, **15**, 624) have discussed this problem. Our own treatment, which was arrived at independently, is practically identical with that of the last-named authors. It can be briefly summarised as follows :

The Langmuir adsorption isotherm for a single type of adsorption location can be expressed in the form given by Fowler (*Proc. Camb. Phil. Soc.*, 1935, **31**, 260) :

$$q_{(1)} = \frac{N_s c\mathrm{A}(T)\mathrm{e}^{\chi/RT}}{[1 + c\mathrm{A}(T)\mathrm{e}^{\chi/RT}]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where χ denotes the heat of adsorption, c the concentration of the solute (or pressure in the case of a gas), N_s the total number of adsorption locations (*e.g.*, per cm.^{2} of surface); $\mathrm{A}(T)$ is a function of the temperature (independent of χ and c) and contains the partition functions of the adsorbed and unadsorbed molecules. For an adsorbent with regions of different adsorption locations one obtains :

$$q = \int_0^\infty \frac{c\mathrm{A}(T)\mathrm{e}^{\chi/RT}}{[1 + c\mathrm{A}(T)\mathrm{e}^{\chi/RT}]} N(\chi)\mathrm{d}\chi \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

if $N(\chi)\mathrm{d}\chi$ is the number of locations with adsorption energies between χ and $(\chi + \mathrm{d}\chi)$.

Assuming that the adsorption energies follow a Boltzmann distribution given (with the proper normalising factor) by

$$N(\chi)\mathrm{d}\chi = (N_s/R\theta)\mathrm{e}^{-\chi/R\theta} \,.\, \mathrm{d}\chi \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $R\theta (= \chi_m)$ can be regarded as the *minimum* mean adsorption energy it can be shown that if this is introduced into equation (2) one obtains finally :

$$q = N_s \frac{RT}{\chi_m}\left\{(\mathrm{A}c)^{RT/\chi_m}\frac{\pi}{\sin\left(\frac{RT\pi}{\chi_m}\right)} - \frac{(\mathrm{A}c)}{\left(1 - \frac{RT}{\chi_m}\right)} + \frac{(\mathrm{A}c)^2}{\left(2 - \frac{RT}{\chi_m}\right)} - \ldots\ldots\right\} \quad . \quad . \quad (4)$$

which for small values of $(\mathrm{A}c)$ reduces to

$$q \sim \left\{N_s \frac{RT}{\chi_m}\mathrm{A}^{RT/\chi_m}\frac{\pi}{\left(\sin\frac{RT\pi}{\chi_m}\right)}\right\} c^{RT/\chi_m} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

This is of the same form as the equation of the Freundlich isotherm ($q = \alpha c^n$) if one puts

$$n = RT/\chi_m = T/\theta$$

$$\alpha = N_s \frac{RT}{\chi_m}\frac{\pi}{\left(\sin\frac{RT\pi}{\chi_m}\right)}\mathrm{A}^{RT/\chi_m}$$

In general, the smaller the adsorption energy (the smaller χ_m), the greater is the exponent n. Small values of n are thus connected with high values of χ_m, which means high adsorption energies, *i.e.*, approaching chemisorption and indicating a chemical process on the surface. On the basis of this theoretical interpretation one can conclude that colour formation is connected with adsorption on centres of high adsorption energy probably involving chemical interaction. A value of RT/χ_m nearer to unity ($\chi_m \sim RT$) would indicate a predominantly "physical" interaction.

The question is as to how these chemical surface reactions can be explained. The formation of benzidine-blue and the oxidation of aromatic amines is relatively easy to understand, as this is obviously due to an oxidation of the amine by lattice-bound metal ions.

The action of aluminosilicates as strong acids in the halochromic colour reactions is less obvious. It can, however, be understood from certain ideas proposed by Pauling (" The Nature of the Chemical Bond ", Cornell University Press, 2nd ed., 1947, p. 396). It is known that the aluminosilicates represent a complete framework of linked tetrahedra involving (Si^{4+}), (Al^{3+}), and (O^{2-}) ions. $Al(OH)_3$ and $Si(OH)_4$ are very weak acids as the O^{2-} is acted upon in each case by a total bond strength of 1 from the central atom thus leaving one full bond strength on the O^- atom for the binding of the hydrogen atom. This is different in the aluminosilicates where one has (Si^{4+} . O^{2-}) tetrahedra with corners shared with Al^{3+} tetrahedra. An (O^{2-}) ion which is common to an (Al^{3+}) and an (Si^{4+}) tetrahedron is thus acted upon by a total bond strength of $(4/4 + 3/4) = 7/4$ bond strengths, leaving only $(2 - 7/4) = 1/4$ for the binding of the hydrogen atom : thus a strong acid results.

On the basis of this simple picture the strength of this acid should be comparable to that of perchloric acid, $HClO_4$, where each oxygen atom is also held by a bond strength of 7/4. Treatment of an alkali salt of the aluminosilicate with acid will liberate the acid and the surface of the acid-treated clay will become strongly proton-donating.

(3) *The Action of Silica–Alumina Catalysts.*—It is know that silica–alumina catalysts, under suitable conditions, can bring about all the types of chemical reaction which are generally associated with catalysts of the nature of a strong acid (*e.g.*, alkylation, dealkylation, cracking, Friedel–Crafts reactions). It is also known that in these processes the first and essential step is the formation of a positive carbonium ion which is formed, *e.g.*, by the addition of a proton from the catalyst. These positive ions are relatively unstable and undergo characteristic changes leading to the reactions mentioned above (cf. Whitmore, *J. Amer. Chem. Soc.*, 1932, **54**, 3276; Hansford, *Ind. Eng. Chem.*, 1947, **39**, 849).

In the case of the silica–alumina catalysts these positive ions are formed on the surface of the catalyst with the protons from the catalyst surface.

It has been shown above that these protons are also responsible for a certain type of colour reaction (*e.g.*, with dicinnamylideneacetone) and it is thus clear that this colour reaction should be a useful indication of the proton-donating properties of the surface and thus of its catalytic activity. Experiments to correlate these two functions are now in progress and will be reported in due course.

Experimental.

Adsorbents used.—Bentonite was from Wyoming, U.S.A., fuller's earth as noted in Table IV, clarit from Messrs. Lever Bros., montmorillonite from the Rhön Mountains, Germany, and kaolin was a commercial sample of unknown origin, labelled " acid washed ".

Treatment of Adsorbents.—" HCl-treated " : the adsorbent was stirred at room temperature with 50—100 vols. of concentrated acid and centrifuged. The treatment was twice repeated and the adsorbent was finally washed with three changes of distilled water.

" HCl-refluxed " : the adsorbent was refluxed for 30—60 mins. with 50—100 vols. of concentrated acid. After cooling, it was washed on the centrifuge first with concentrated hydrochloric acid, then several times with distilled water. NH_3-treated : a sample which had previously been treated with hydrochloric acid was stirred for 30 mins. at room temperature with 50—100 vols. of N-NH_3, centrifuged, and washed with several changes of 10% ammonium acetate on the centrifuge.

" $SnCl_4$-treated " : the adsorbent was refluxed for 30—60 mins. with 50—100 vols. of 10% solution of stannous chloride in concentrated hydrochloric acid. After cooling it was washed on the centrifuge first with concentrated acid, then several times with distilled water.

All adsorbents were dried at 120° for about 12 hours, ground to a fine powder and passed through a 150-mesh sieve. They were stored over anhydrous calcium chloride.

Substrates.—Vitamin-A solutions were prepared by dissolving the content of one " Adexolin " capsule (Glaxo Ltd.) in about 50 ml. of benzene. Dicinnamylideneacetone was prepared by the method of Baeyer and Villiger (*Ber.*, 1905, **38**, 582); it produced a deep violet colour. 4-Amino-2′ : 3-azotoluene was a recrystallised commercial preparation; it produced a purple colour on acid clays. Benzidine was purified by conversion into the hydrochloride, recrystallisation from water, regeneration of the base, and recrystallisation from 95% ethanol.

Other substrates used for colour tests were : β-carotene (Roche Products Ltd.) (blue colour); 2-amino-4′ : 5-azotoluene (green colour); *p*-dimethylaminoazobenzene (red colour); anisylideneacetone (red colour); dianisylideneacetone (purple colour); dibenzylideneacetone (yellow colour).

Adsorption Isotherms.—For each test four samples of adsorbents, weighing roughly 10, 30, 100, and 200 mg., were filled into tared 10-ml. ampoules, dried overnight at 120°, and weighed. Five ml. of a solution of the substrate in benzene, usually containing 0·5, 1·5, or 15 mg., were added. The ampoules were sealed and shaken at room temperature (18—20°) for 4—5 hours. The concentration of the supernatant solution was then determined by the following methods : Aminoazotoluene was determined by direct colorimetry of the original benzene solution. Dicinnamylideneacetone : an aliquot of the benzene solution containing between 10 and 100 g. was evaporated to dryness in a vacuum and 10 ml.

of a saturated solution of antimony trichloride in chloroform (dry and free from ethanol) were added. Determination by colorimetry followed. Benzidine: an aliquot of the benzene solution containing 10—100 μg. was evaporated to dryness in a vacuum and taken up in 2 ml. of 0·2N-hydrochloric acid. After diazotisation and coupling with *N*-(1-naphthyl)ethylenediamine dihydrochloride according to Klein (*Ind. Eng. Chem. Anal.*, 1944, **16**, 536) a colorimetric estimation was carried out.

All absorption measurements were done photoelectrically with the aid of suitable filters after calibration curves had been established with standard solutions.

Our thanks are due to Dr. G. Nagelschmidt, English Clays Lovering Pochin Co. Ltd., for supplying some of the clay minerals used in this investigation.

UNIVERSITY OF DURHAM,
KING'S COLLEGE, NEWCASTLE-ON-TYNE, 1. [*Received, February 14th*, 1948.]

---

437. *Products of Nitration of Some Derivatives of Dimethylaniline, Auramine, and Crystal-violet.*

By S. GALINOWSKI and T. URBAŃSKI.

Nitration of auramine yields 3 : 5 : 3′ : 5′-tetranitro-4 : 4′-bismethylnitroaminobenzophenone previously obtained by Van Romburgh (*Rec. Trav. chim.*, 1887, **6**, 368) by nitration of Michler's ketone.

Nitration of crystal-violet yields 3 : 5 : 3′ : 5′ : 3″ : 5″-*hexanitro*-4 : 4′ : 4″-*trismethylnitroaminotriphenylcarbinol*; this, under the action of dilute alkalis or acetic anhydride, loses a molecule of nitric acid and yields a corresponding quinoneimine which, with addition of nitric acid, regenerates the original carbinol.

If auramine is nitrated by adding a solution of its hydrochloride in sulphuric acid to an excess of concentrated nitric acid, a crystalline product is precipitated, which is identical with 3 : 5 : 3′ : 5′-tetranitro-4 : 4′-bismethylnitroaminobenzophenone, prepared by Van Romburgh (*loc. cit.*) by nitration of Michler's ketone. Hence, it is evident that in the course of the nitration the imino-group of auramine is hydrolysed to the carbonyl group.

The same result was obtained when nitration was carried out in presence of acetic anhydride or phosphoric oxide instead of sulphuric acid. Also acetylation of the imino-group with acetic anhydride before nitration does not prevent this group from being transformed into a carbonyl group. Further, we attempted unsuccessfully to form a nitroimino-group by the action of dehydrating agents, such as acetic anhydride alone or with sulphuric acid, zinc chloride, or phosphoric oxide on auramine nitrate.

The nitration of crystal-violet was carried out by dissolving the sulphate of the base in concentrated sulphuric acid and adding the solution to concentrated nitric acid. A strongly exothermic reaction accompanied by gas-evolution occurs, and crystalline 3 : 5 : 3′ : 5′ : 3″ : 5″-*hexanitro*-4 : 4′ : 4″-*trismethylnitroaminotriphenylcarbinol* (I) is precipitated. This substance is acidic and gives a sodium salt on reaction with sodium methoxide.

The colourless product (I) or its sodium salt, boiled with dilute sodium hydroxide, furnishes the yellow quinonoid *compound* (II) and a substance soluble in alkalis, probably 3 : 5 : 3′ : 5′ : 3″ : 5″-hexanitroaurin (III). The proportion of the products (II) and (III) varies according to the concentration of the alkali with which (I) is boiled: the lower this concentration the higher the proportion of (II).

The formation of (II) is accompanied by that of sodium nitrate. This, however, was obscured by the simultaneous formation of (III) and of sodium nitrate and nitrite and methylamine.

The imide (II) can be prepared from (I) by boiling it with acetic anhydride. This is accompanied by strong evolution of nitrogen and carbon dioxide, probably owing to the reaction between nitric acid and acetic anhydride at high temperature.

Both products (I) and (II) were oxidised by chromic anhydride in presence of acetic anhydride and furnished 3 : 5 : 3′ : 5′-tetranitro-4 : 4′-bismethylnitroaminobenzophenone (above).

(I.) $OH{\cdot}C[C_6H_2(NO_2)_2{\cdot}NMe{\cdot}NO_2]_2$

(II.) $NMe{:}C_6H_2(NO_2)_2{:}C[C_6H_2(NO_2)_2{\cdot}NMe{\cdot}NO_2]_2$ (III.) $OH{\cdot}C[C_6H_2(NO_2)_2{\cdot}OH]_2$

The product (II) is soluble in methyl-alcoholic sodium methoxide and can be precipitated unchanged by acidifying the solution with dilute acid.

EXPERIMENTAL.

Nitration of Auramine.—Auramine hydrochloride monohydrate (20 g.) was dissolved in concentrated sulphuric acid (100 g.) and the solution was added dropwise during *ca.* 1 hour with stirring to anhydrous

nitric acid (100 g.) at 60—70°. The reaction proceeds with evolution of gas and precipitation of 3 : 5 : 3′ : 5′-tetranitro-4 : 4′-bismethylnitroaminobenzophenone (27 g., 85%). Crystallised thrice from nitrobenzene and benzene or from concentrated nitric acid, it had m. p. 200°, unchanged when mixed with the product prepared according to Van Romburgh from Michler's ketone (Found: C, 35·3; N, 21·5. Calc. for $C_{15}H_{10}O_{12}N_8$: C, 35·3; N, 21·9%).

3 : 5 : 3′ : 5′ : 3″ : 5″-*Hexanitro*-4 : 4′ : 4″-*trismethylnitroaminotriphenylcarbinol* (I).—Crystal-violet hydrochloride (13 g., 100% purity) was dissolved in concentrated sulphuric acid (100 g.), and the solution added dropwise during 2 hours with stirring to anhydrous nitric acid (150 g.) at 60—70°. The crystalline *product* (I) was precipitated, and was filtered off, washed, dried (22—24 g., 88—96%), and recrystallised from nitric acid (*d* 1·50); decomp. 228° (capillary tube) [Found: C, 34·3; H, 2·7; N, 22·7; NO_2 (nitrometer), 18·3. $C_{22}H_{16}O_{18}N_{12}$ requires C, 35·1; H, 2·1; N, 22·3; NO_2 (nitroamine), 18·4%].

Sodium salt. The substance (I) was suspended in methyl alcohol and a 5% solution of sodium methoxide in methyl alcohol was added dropwise with stirring until complete solution of (I) took place. A small excess of (I) was then added to avoid any excess of methoxide, and the solution was filtered and evaporated under reduced pressure. A brown sodium salt remained. It was not analysed as it could not be purified from any solvent. On reaction with hydrochloric acid, it regenerated (I).

Action of Alkalis on (I).—The substance (I) (37 g.) was boiled with a 2% solution of potassium hydroxide by injecting steam for 30 minutes. The vapours were trapped in dilute hydrochloric acid. The liquid turned brown, methylamine distilled over, and the yellow suspension of 2 : 6-*dinitro*-4-*bis*-(3′ : 5′-*dinitro*-4′-*methylnitroaminophenyl*)*methylene*-N-*methylsemiquinone* (II) was filtered off (16 g.). Crystallised from acetic acid, it had m. p. 210° (decomp.) [Found: C, 39·5; H, 2·7; N, 21·5; NO_2 (nitrometer), 13·0. $C_{22}H_{15}O_{16}N_{11}$ requires C, 38·3; H, 2·2; N, 22·3; NO_2 (nitroamine), 13·3%].

Examination of the By-products of the Formation of (II).—The filtrate from (II) was acidified with hydrochloric acid and a precipitate, possibly 3 : 5 : 3′ : 5′ : 3″ : 5″-hexanitroaurin (III) (10 g.) was filtered off. It could not be satisfactorily purified and was not analysed. When heated (8 g.) with nitric acid (*d* 1·50) at 100° for 20 hours it yielded picric acid (1·5 g.). The filtrate from (III) contained nitrous and nitric acid.

Action of Acetic Anhydride on the Product (I).—The substance (I) (50 g.) was boiled under reflux with acetic anhydride (250 c.c.) for 6 hours. Evolution of nitrogen and carbon dioxide (3·3 l.) occurred. The product (II) (35 g.), which crystallised after addition of water (50 c.c.), was identical with that prepared as described above.

Oxidation of (I) *or* (II).—The substance (I) or (II) (20 g.) was boiled for 10 mins. with acetic anhydride (100 c.c.) and then a solution of chromic anhydride (10 g.) in acetic anhydride (50 c.c.) was added dropwise, and the whole boiled for 30 minutes. The resulting solution was poured into water, and the precipitate filtered off, and identified as 3 : 5 : 3′ : 5′-tetranitro-4 : 4′-bismethylnitroaminobenzophenone.

The authors thank the Director General of Scientific Research (Defence), Ministry of Supply, for permission to publish the work.

ARMAMENT RESEARCH DEPARTMENT,
ROYAL ARSENAL, WOOLWICH.

[*Received, February 16th*, 1948.]

---

438. *Alkaloids of* Daphnandra *Species. Part I. Repandine.*

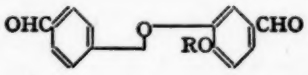
By I. R. C. BICK and A. R. TODD.

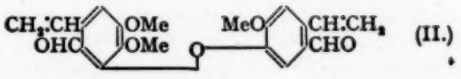
Repandine, $C_{37}H_{40}O_6N_2$, an alkaloid from *D. repandula*, is shown to have structure (III; R = H) or (IV; R = H) and to be an optical isomer of oxyacanthine. Bisbenzyl*iso*quinoline alkaloids have not hitherto been reported in plants of the family *Monimiaceæ*. Repandine is also shown to be identical with a base obtained in small amount by v. Bruchhausen and Schulze (*Arch. Pharm.*, 1929, **267**, 623) from a specimen of oxyacanthine and believed by them to be an artefact. It is considered that, in fact, traces of repandine occur together with oxyacanthine in at least one *Berberis* species.

TREES belonging to the genus *Daphnandra* (family *Monimiaceæ*) are native to Australia and occur in coastal regions of Queensland and northern New South Wales. The presence of alkaloids in the bark of *Daphnandra* species was first reported by Bancroft (*J. Proc. Roy. Soc. N.S.W.*, 1886, **20**, 69; *Proc. Roy. Soc. Queensland*, 1887, **4**, 13; *Austr. J. Pharm.*, 1887, **2**, 103), and much later Pyman (*J.*, 1914, **105**, 1679) isolated three alkaloids daphnandrine, $C_{38}H_{38}O_6N_2$, daphnoline, $C_{35}H_{36}O_6N_2$ or $C_{34}H_{34}O_6N_2$, and micranthine, $C_{36}H_{32}O_6N_2$, from *D. micrantha*. Beyond characterisation, analysis and a description of certain colour reactions, no chemical investigation of these substances appears to have been made, although Pyman (*loc. cit.*) records a pharmacological examination by Dale which showed them to have relatively low toxicity. Recently, the remaining three species have been examined by Bick and Whalley (Univ. of Queensland Papers, Dept. of Chemistry, 1946, **1**, No. 28; 1947, **1**, No. 30; 1948, **1**, No. 32, in the press). These workers isolated from *D. repandula* two new alkaloids, repanduline, $C_{40}H_{46}O_8N_2$, and repandine, $C_{38}H_{42}O_6N_2$, from *D. Dielsii* repanduline and from *D. aromatica* daphnoline, and a third new alkaloid of formula $C_{36}H_{38}O_6N_2$ which they named aromoline. Some years ago one of us (A. R. T.) in collaboration with Dr. E. S. Ewen commenced a study of

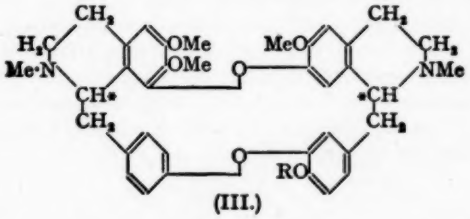
the alkaloids of *D. micrantha* using the material isolated by the late Dr. Pyman and kindly supplied by him. This study was left unfinished as a result of war circumstances, but material for a more comprehensive investigation being now available the present authors have taken it up again and extended it to cover in addition the new alkaloids isolated by Bick and Whalley (*loc. cit.*). The earlier study above mentioned had revealed that daphnandrine and daphnoline were almost certainly members of the bisbenzyl*iso*quinoline group; from the published molecular formulæ it seemed very probable that, apart perhaps from repanduline, the other *Daphnandra* bases were also members of this group, and this determined from the outset the degradative methods applied to repandine, whose structure forms the subject of the present memoir. The results of investigations on daphnandrine and the other alkaloids from *Daphnandra* species will be reported later.

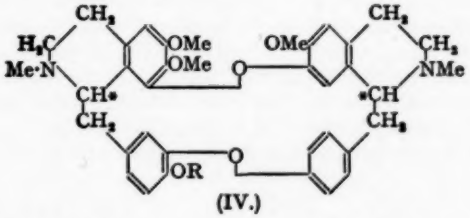
As a result of further analyses, the molecular formula of repandine given by Bick and Whalley (*loc. cit.*) has been modified to $C_{37}H_{40}O_6N_2$. The presence of three methoxy- and two methylimino-groups was confirmed, and it was found that repandine has weak phenolic properties. Methylation of repandine with methyl iodide in methanolic sodium methoxide yielded O-*methylrepandine dimethiodide*; Hofmann degradation of this product gave *O*-methylrepandinemethine, isolated as its dimethiodide. When ozonised, the methine base, which was optically inactive, yielded 2-methoxydiphenyl ether-5 : 4′-dialdehyde (I; R = Me) and an amino-aldehyde, which

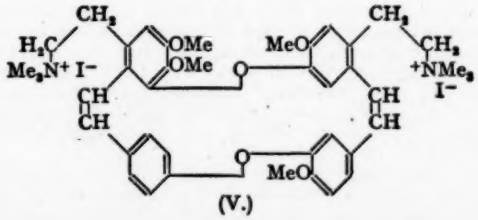
(I.) 

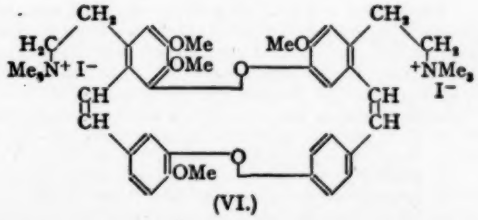

(II.)

was converted into its methiodide in the usual manner and submitted to a further Hofmann degradation. The product was a crystalline aldehyde, identified as 2 : 3 : 2′-trimethoxy-5 : 4′-divinyldiphenyl ether-6 : 5′-dialdehyde (II) by direct comparison with an authentic specimen prepared from oxyacanthine by an analogous series of reactions (v. Bruchhausen and Gericke, *Arch. Pharm.*, 1931, **269**, 115). The isolation of the two aldehydes above mentioned shows that *O*-methylrepandine belongs to the bisbenzyl*iso*quinoline group of bases and must have structure (III; R = Me) or (IV; R = Me), whilst *O*-methylrepandinemethine dimethiodide must be correspondingly represented by (V) or (VI).


(III.)


(IV.)


(V.)


(VI.)

Repandine is isomeric with oxyacanthine and with berbamine, both alkaloids isolated from various *Berberidaceæ*. Of formulæ (III; R = Me) and (IV; R = Me), one also represents *O*-methyloxyacanthine and the other *O*-methylberbamine (v. Bruchhausen and Gericke, *loc. cit.*).

In this series, mixed melting points are not wholly satisfactory as a means of establishing the identity of compounds derived from different sources and recourse was had to the method of *X*-ray powder photography. It was found that the powder photographs of *O*-methylrepandinemethine dimethiodide (V or VI) and *O*-methyloxyacanthinemethine dimethiodide (V or VI; v. Bruchhausen and Gericke, *loc. cit.*) were identical. It follows therefore that repandine corresponds to oxyacanthine rather than to berbamine in its structure. Examination of *X*-ray powder photographs and optical rotations, however, showed that *O*-methylrepandine dimeth-

iodide was not identical with *O*-methyloxyacanthine dimethiodide; clearly *O*-methylrepandine (III; R = Me or IV; R = Me) must differ from *O*-methyloxyacanthine in the stereochemical arrangement about one or other of the asymmetric centres marked with asterisks.

In order to determine the location of the phenolic hydroxyl in repandine, the alkaloid, which could not be satisfactorily ethylated with diazoethane, was converted into its resinous dimethiodide and the latter ethylated to give O-*ethylrepandine dimethiodide*. When this product was submitted to Hofmann degradation, and the resulting methine base ozonised, an aldehyde was isolated which gave the expected analytical values for 2-*ethoxydiphenyl ether-5 : 4′-dialdehyde* (I; R = Et) and when oxidised gave an acid corresponding in its properties to 2-ethoxydiphenyl ether-5 : 4′-dicarboxylic acid previously obtained by Späth and Pikl (*Ber.*, 1929, **62**, 2251) in similar fashion from *O*-ethyloxyacanthine.

It follows, therefore, that repandine has structure (III; R = H) or (IV; R = H) and is an optical isomer of oxyacanthine. Four isomers are possible for each of the structures (III) and (IV), and if we assume that their optical rotation is due to the summation of two components A and B corresponding to each of the two asymmetric centres, then of the four possibilities A + B, A − B, −A + B, and −A − B (where A is assumed to be greater than B), the first evidently represents oxyacanthine ($[\alpha]_D = +279°$) and the third repandine ($[\alpha]_D^{15°} = -106°$). On this basis A would be *ca.* 190° and B *ca.* 85° in the oxyacanthine group. It is interesting to note that, of the four isomers possible in the berbamine series, berbamine itself is the only one known to occur naturally; of the corresponding methyl ethers, however, three occur (Kondo and Keimatsu, *Ber.*, 1935, **68**, 1503), *viz.*, phaeanthine ($[\alpha]_D^{20°} = -278°$), its enantiomorph tetrandrine ($[\alpha]_D^{24°} = +263°$) and *iso*tetrandrine (*O*-methylberbamine) ($[\alpha]_D^{17°} = +146°$). The fact that repandine is a bisbenzyl*iso*quinoline alkaloid is of some botanical interest since no alkaloid of this group has hitherto been reported either in the *Monimiaceæ* or in the related *Lauraceæ*.

The properties of repandine agree closely with those recorded for a base, m. p. 255° ($[\alpha]_D^{20°} = -95°$), isolated from a sample of oxyacanthine by v. Bruchhausen and Schulze (*loc. cit.*) during an attempt to prepare a monohydrochloride of the latter substance; the new base was considered by these workers to be an artefact produced from oxyacanthine during treatment with hydrogen chloride. Through the kindness of Prof. v. Bruchhausen we have been able to establish the identity of repandine with this base by direct comparison; the two materials showed no m. p. depression on mixing and their Debye–Scherrer diagrams were identical. In view of the relationship between repandine and oxyacanthine established in the present investigation, we consider it very improbable that it could be produced from oxyacanthine by treatment with hydrogen chloride, and indeed we could obtain no evidence of its formation from purified oxyacanthine in these circumstances. We therefore conclude that it did not arise as an artefact in the experiments of v. Bruchhausen and Schulze (*loc. cit.*) and that repandine actually occurs in small amount along with oxyacanthine in at least one species of *Berberis*.

Experimental.

Repandine.—A specimen of the alkaloid isolated from *D. repandula* (Bick and Whalley, *loc. cit.*) was purified by repeated recrystallisation from acetone and ethanol and formed colourless needles, m. p. 255°, $[\alpha]_D^{15°}$ −106° (*c*, 1·2 in chloroform). It gave no coloration with ferric chloride but gave a pink colour with Millon's reagent. On addition of excess of alkali to a solution of the base in dilute hydrochloric acid (5%) the precipitate first formed redissolved to a clear solution; on passing carbon dioxide through this solution a white precipitate was produced which after recrystallisation from ethanol had m. p. 255°, undepressed by the original repandine (Found: C, 72·9; H, 6·9; N, 4·7; MeO, 15·2; MeN, 9·3. Calc. for $C_{37}H_{40}O_6N_2$: C, 73·0; H, 6·6; N, 4·6; 3MeO, 15·3; 2MeN, 9·5%).

O-*Methylrepandine Dimethiodide.*—Repandine (5 g.) was dissolved in dry methanol (200 c.c.) and methyl iodide (7·5 c.c.) was added, followed by methanolic sodium methoxide (0·32 g. of sodium in 5 c.c. of methanol). The mixture was refluxed for 6 hours, a similar amount of sodium methoxide added, and heating continued for a further 6 hours; this process was repeated until in all five such additions of sodium methoxide had been made. The solution was then evaporated under reduced pressure, and the residue taken up in hot water. The aqueous solution on cooling deposited an amorphous solid which was collected and redissolved in hot water, and the solution was boiled with a little copper powder during ten minutes, filtered, and set aside. The *dimethiodide* slowly crystallised as colourless needles (6·1 g.) which decomposed at 255—260° without melting, $[\alpha]_D^{15°}$ −95° (*c*, 0·3 in 50% aqueous ethanol) (Found: C, 48·4; H, 5·8; N, 2·6; I, 26·0; loss at 110°/0·1 mm., 9·3. $C_{40}H_{48}O_6N_2I_2,5H_2O$ requires C, 48·2; H, 5·9; N, 2·8; I, 25·5; $5H_2O$, 9·0%). *O*-Methyloxyacanthine dimethiodide had $[\alpha]_D^{16°} = +40°$ (*c*, 0·4 in 50% aqueous ethanol) (Gadamer and v. Bruchhausen, *Arch. Pharm.*, 1926, **264**, 193, give $[\alpha]_D = +42°$).

O-*Methylrepandinemethine Dimethiodide.*—*O*-Methylrepandine dimethiodide (5 g.) was dissolved in water (1 l.) and shaken with freshly prepared silver oxide (from 5 g. of silver nitrate). After 1 hour the solution, which was free from iodide ions, was filtered and concentrated to 100 c.c. under reduced pressure. Aqueous potassium hydroxide (50 c.c. of 50%) was now added, and the mixture heated on

the steam-bath for 2 hours during which time a yellowish resin slowly separated. The cooled mixture was extracted with chloroform, and the combined extracts were washed with water and dried (Na_2SO_4). On evaporation of the chloroform solution the methine base was obtained as a yellowish resin (2·5 g.) which could not be crystallised. For characterisation a portion of the resin (1 g.) was dissolved in methanol (50 c.c.) and refluxed with methyl iodide (1 c.c.) during 15 minutes. On concentrating the resulting solution to small bulk *O*-methylrepandinemethine dimethiodide separated and was recrystallised from methanol. Colourless needles, m. p. 255—260° (decomp.), identical (Debye–Scherrer diagram) with *O*-methyloxyacanthinemethine dimethiodide (m. p. 255—260°, decomp.) (Found: C, 52·2; H, 6·1; N, 3·1; loss at 110°/0·1 mm., 4·6. Calc. for $C_{42}H_{52}O_6N_2I_2,2H_2O$: C, 52·0; H, 5·8; N, 2·9; $2H_2O$, 3·9%).

Ozonolysis of O-*Methylrepandinemethine.*—The above resinous methine (3·1 g.) was dissolved in dilute sulphuric acid (20 c.c. of 5%), and a stream of ozone passed through the ice-cold filtered solution for 30 minutes. The yellowish resin which separated was extracted with ether; further passage of ozone through the aqueous solution left after extraction yielded only a small additional quantity of product, which was likewise extracted with ether. The combined ether extracts were washed, dried (Na_2SO_4), and evaporated. Recrystallisation of the residue from light petroleum (b. p. 40—60°) gave colourless prismatic needles (0·9 g.), m. p. 77—78° (Found: C, 70·2; H, 4·7; MeO, 11·4. Calc. for $C_{15}H_{12}O_4$: C, 70·3; H, 4·7; MeO, 12·1%). A mixed m. p. with 2-methoxydiphenyl ether-5 : 4′-dialdehyde (m. p. 77—78°) prepared by a similar series of reactions from oxyacanthine showed no depression.

The acid aqueous solution obtained after ozonolysis and extraction with ether was shaken for 15 minutes with palladised charcoal (0·1 g.) to remove peroxides, then shaken with hydrogen for a further 15 minutes and made alkaline with sodium hydroxide. The precipitated amino-aldehyde was extracted with ether, and the extract dried and evaporated. The residue was dissolved in methanol (10 c.c.), methyl iodide (2 c.c.) added, and the solution refluxed for 15 minutes. On concentration of the solution the amino-aldehyde dimethiodide separated as colourless needles (2·8 g.) and was recrystallised from aqueous methanol. On heating it melted with decomposition between 230° and 240° (Found: C, 43·0; H, 5·8; N, 3·8; loss at 110°/0·1 mm., 3·0. Calc. for $C_{27}H_{38}O_6N_2I_2,H_2O$: C, 42·6; H, 5·6; N, 3·7; H_2O, 2·4%).

2 : 3 : 2′-*Trimethoxy*-5 : 4′-*divinyldiphenyl Ether*-6 : 5′-*dialdehyde.*—The above amino-aldehyde dimethiodide (2·5 g.) was dissolved in water (100 c.c.) and shaken for 3 hours with freshly prepared silver oxide (from 2 g. of silver nitrate). The mixture was filtered, the filtrate concentrated to small bulk, and aqueous potassium hydroxide (20 c.c. of 50%) added. The alkaline solution was heated on the steam-bath until no more trimethylamine was evolved. The yellowish resin which separated was extracted with chloroform, and the extract washed, dried, and evaporated to small bulk. On standing, 2 : 3 : 2′-trimethoxy-5 : 4′-divinyldiphenyl ether-6 : 5′-dialdehyde separated in almost colourless diamond-shaped crystals (0·9 g.). Recrystallised from chloroform it had m. p. 139°, undepressed in admixture with an authentic specimen (m. p. 139°) prepared from oxyacanthine. On catalytic hydrogenation the substance took up 2 mols. of hydrogen rapidly and a further 2 mols. more slowly (Found: C, 68·6; H, 5·4; MeO, 24·5. Calc. for $C_{21}H_{20}O_6$: C, 68·5; H, 5·5; 3MeO, 25·3%).

O-*Ethylrepandine Dimethiodide.*—Repandine (2 g.) was dissolved in hot methanol (100 c.c.) and refluxed with methyl iodide (2 c.c.) for 15 minutes. Removal of solvents under reduced pressure gave the dimethiodide as a yellowish resin which could not be crystallised. The resin was dissolved in hot ethanol (200 c.c.), and ethyl iodide (5 c.c.) added followed by ethanolic sodium ethoxide (0·12 g. of sodium in 4 c.c. of ethanol). The mixture was refluxed for 6 hours, when a further similar amount of sodium ethoxide was added and heating continued. The process was repeated until 5 such quantities of sodium ethoxide had been added. The resulting solution was evaporated under reduced pressure, and the residue dissolved in hot water. A brownish resin separated on cooling; it was redissolved in hot water, and the solution boiled with copper powder for 10 minutes, filtered, and cooled. O-*Ethylrepandine dimethiodide* separated as a white amorphous mass (2 g.). Purified by being allowed to separate from hot water, it melted with decomposition between 235° and 245° (Found: C, 51·3; H, 5·7; N, 3·0; loss at 110°/0·1 mm., 5·1. $C_{41}H_{50}O_6N_2I_2,2\frac{1}{2}H_2O$ requires C, 51·0; H, 5·7; N, 3·0; H_2O, 4·7%).

2-*Ethoxydiphenyl Ether*-5 : 4′-*dialdehyde.*—*O*-Ethylrepandine dimethiodide (1·5 g.) was submitted to Hofmann degradation in the manner described above for the corresponding *O*-methyl compound. The crude methine base was dissolved in ice-cold dilute sulphuric acid and ozonised during 30 minutes. The resin which separated was taken up in ether, and the extract washed, dried (Na_2SO_4), and evaporated. The residue crystallised from ether–light petroleum as colourless prismatic needles, m. p. 59—60° (Found: C, 70·8; H, 5·4; EtO, 16·3. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2; EtO, 16·7%). Admixture with 2-methoxydiphenyl ether-5 : 4′-dialdehyde (above) gave a depression in m. p. of *ca.* 10°.

The *dialdehyde*, oxidised with potassium permanganate in acetone solution, gave an acid crystallising from glacial acetic acid in needles, m. p. 287° (Found: C, 63·2; H, 5·2. Calc. for $C_{16}H_{14}O_6$: C, 63·6; H, 4·7%). Späth and Pikl (*loc. cit.*) record m. p. 288·5—289·5° for 2-ethoxydiphenyl ether-5 : 4′-dicarboxylic acid.

We wish to express our gratitude to Prof. F. von Bruchhausen and Prof. F. von Wessely for their gifts of samples of oxyacanthine and certain of its degradation products, and to the British Council for a scholarship held by one of us (I. R. C. B.). We are also deeply indebted to Dr. P. J. G. de Vos who carried out the *X*-ray crystallographic examinations.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 18th,* 1948.]

439. *Amines containing 2-Halogenoethyl Groups.*

By A. F. Childs, L. J. Goldsworthy, G. F. Harding, F. E. King, A. W. Nineham, W. L. Norris, S. G. P. Plant, B. Selton, and A. L. L. Tompsett.

Studies have been made of compounds related to the known vesicant bases, methyldi-(2-chloroethyl)amine and tri-(2-chloroethyl)amine. The *substances* $NR(CH_2{\cdot}CH_2Cl)_2$ (R = Ac, $CH_2Cl{\cdot}CO$, CO_2Me, CN, Cl·CO, and $CH_2{\cdot}OMe$) have been made from di-(2-chloroethyl)amine, while attempts to introduce the *n*-butoxymethyl group into the base led to the isolation of *NN'-di-(2-chloroethyl)piperazine*. The synthetical work has been extended by the preparation of *NNN'N'-tetra-(2-chloroethyl)ethylenediamine*, *tri-(2-chloroethylthioethyl)amine hydrochloride*, and *tri-(2-bromoethyl)amine*. Fluorine analogues of the above bases which have been prepared include *di-(2-fluoroethyl)amine*, *methyldi-(2-fluoroethyl)amine*, *tri-(2-fluoroethyl)amine*, *2-chloroethyldi-(2-fluoroethyl)amine*, and *di-(2-chloroethyl)-2-fluoroethylamine*. Several derivatives of these fluorine-containing bases have been made.

In the preparation of the substances described below, which are related to the vesicant bases, methyldi-(2-chloroethyl)amine and tri-(2-chloroethyl)amine, the formation of *NN'-di-(2-chloroethyl)piperazine* requires special comment. Stewart and Bradley (*J. Amer. Chem. Soc.*, 1932, **54**, 4172) have described the preparation of *n*-butoxymethyldiethylamine, $Et_2N{\cdot}CH_2{\cdot}OC_4H_9$, from diethylamine, *n*-butanol, and paraformaldehyde under anhydrous conditions. In attempts to prepare an analogous compound similarly from di-(2-chloroethyl)amine, the only substance isolated was *NN'-di-(2-chloroethyl)piperazine dihydrochloride*, from which the base was readily obtained. It is obvious that the dihydrochloride arose from the polymerisation of the di-(2-chloroethyl)amine used, but several attempts to obtain the salt under simpler conditions from the amine alone or in *n*-butanol gave less satisfactory results. Although the instability of di-(2-chloroethyl)amine has been noted (Prelog, Driza, and Hanousek, *Chem. Zentr.*, 1932, i, 1532; Mann, *J.*, 1934, 461), there appears to be no record of any investigation of the polymerisation process.

Experimental.

N-Acetyl-, N-Chloroacetyl-, and N-Carbomethoxy-di-(2-chloroethyl)amine.—A solution of di-(2-chloroethyl)amine hydrochloride (35·7 g., prepared either by the method of Mann, *loc. cit.*, or by that of Ward, *J. Amer. Chem. Soc.*, 1935, **57**, 914) in water (100 c.c.) was treated with sodium hydroxide (8 g.), also dissolved in water (50 c.c.), at 0°. Acetyl chloride (20 g.), diluted with chloroform (30 c.c.), and a solution of sodium hydroxide (10 g.) in water (100 c.c.) were added simultaneously with vigorous stirring during an hour, the temperature being kept between 0° and 5°. The chloroform layer and further chloroform extracts were united, dried (Na_2SO_4), and fractionated. *N-Acetyldi-(2-chloroethyl)amine* (22 g.) was collected as a colourless syrup, b. p. 130—135°/0·2 mm. (152—156°/16 mm.) (Found: C, 38·8; H, 6·1. $C_6H_{11}ONCl_2$ requires C, 39·1; H, 6·0%).

N-Chloroacetyldi-(2-chloroethyl)amine (Found: C, 33·0; H, 4·4. $C_6H_{10}ONCl_3$ requires C, 33·0; H, 4·6%), a colourless oil, b. p. 160—164°/0·2 mm., was similarly prepared from chloroacetyl chloride; and *N-carbomethoxydi-(2-chloroethyl)amine* (Found: C, 36·1; H, 5·5; Cl, 35·2. $C_6H_{11}O_2NCl_2$ requires C, 36·0; H, 5·5; Cl, 35·5%), a colourless oil, b. p. 86—90°/0·06 mm., from methyl chloroformate.

Di-(2-chloroethyl)cyanamide.—An ice-cold solution of di-(2-chloroethyl)amine hydrochloride (53·6 g.) in water (50 c.c.) was shaken with a cold solution of potassium hydroxide (17 g.) in water (30 c.c.), and the oily base was taken up in ether. The ethereal extract was dried ($MgSO_4$) and filtered, and the magnesium sulphate was washed with more ether. Cyanogen bromide (15·9 g.) in dry ether (30 c.c.) was gradually added, with shaking and cooling in ice-water, to the ethereal solution of the base. The reaction (compare Wallach, *Ber.*, 1899, **32**, 1872) was completed within a few minutes with the separation of di-(2-chloroethyl)amine hydrobromide. This was removed by filtration, the filtrate fractionated, and *di-(2-chloroethyl)cyanamide* collected at 135°/0·15 mm. (Found: C, 34·1; H, 4·8; N, 16·6; Cl, 39·1. $C_5H_8Cl_2N_2$ requires C, 35·9; H, 4·8; N, 16·8; Cl, 42·5%).

N-Chloroformyldi-(2-chloroethyl)amine.—A solution of di-(2-chloroethyl)amine in dry benzene (400 c.c.), obtained from the hydrochloride (21 g.) by a process similar to that used for the ethereal solution described above, was cooled in a freezing mixture, and added gradually during ½ hour with mechanical stirring to carbonyl chloride (7·3 g.) dissolved in benzene (100 c.c.), the temperature being kept below 10°. After the mixture had been left for several hours, the precipitate of di-(2-chloroethyl)amine hydrochloride was removed by filtration, and the benzene distilled off on the water-bath. When the residue was distilled under reduced pressure, *N-chloroformyldi-(2-chloroethyl)amine* was obtained as a pale yellow oil (6·8 g.), b. p. 92—96°/0·1 mm. (Found: C, 29·8; H, 4·2; Cl, 52·2. $C_5H_8ONCl_3$ requires C, 29·3; H, 3·9; Cl, 52·1%).

Methoxymethyldi-(2-chloroethyl)amine.—A solution of di-(2-chloroethyl)amine in dry chloroform (60 c.c.) was made from the hydrochloride (17·9 g.) as above. Methoxymethyl chloride (8·4 g., prepared as described by Wedekind, *Ber.*, 1903, **36**, 1383) in chloroform (20 c.c.) was added during ½ hour to a mixture of the chloroform solution of the base and an excess of powdered, dry potassium carbonate which was rapidly stirred and cooled in ice-water. After stirring had been continued for a further 2 hours without cooling, the potassium chloride and potassium carbonate were removed by filtration, and the chloroform distilled off under reduced pressure. When the residue was distilled, a considerable amount of solid was formed in the flask, but *methoxymethyldi-(2-chloroethyl)amine* was collected as a colourless oil, b. p. 106—108°/13 mm. (Found: C, 39·2; H, 7·0; N, 7·7; Cl, 37·2. $C_6H_{13}ONCl_2$ requires

C, 38·7; H, 7·0; N, 7·5; Cl, 38·2%). The base was unstable, and gradually changed into a colourless solid.

NN'-*Di*-(2-*chloroethyl*)*piperazine*.—A mixture of di-(2-chloroethyl)amine (28 g., obtained from its dry ethereal solution by evaporation under reduced pressure), *n*-butanol (18·8 g.), and paraformaldehyde (6 g.) was slowly warmed to 35°. At this point the temperature of the reaction mixture rose to 39·5°, and the whole was left to cool overnight. After potassium carbonate (6 g.) had been added and the mixture left for a further 24 hours, the solid was removed by filtration, and the pale yellow, viscous filtrate was heated to 80° under reduced pressure to remove *n*-butanol. The residue soon solidified, and, after it had been ground with warm alcohol, NN'-*di*-(2-*chloroethyl*)*piperazine dihydrochloride* (4·5 g.), m. p. 315° (decomp.), remained in a pure condition. It separated from aqueous alcohol in colourless prisms (Found: Cl′, 24·9, 25·1; total Cl, 50·7, 51·7. $C_8H_{16}N_2Cl_2,2HCl$ requires Cl′, 25·0; total Cl, 50·0%). When the dihydrochloride was dissolved in the minimum quantity of water at room temperature, and the solution filtered and treated with concentrated aqueous potassium carbonate, NN'-*di*-(2-*chloroethyl*)*piperazine* separated as an oil which rapidly solidified. It was dried in a desiccator, freed from a little inorganic material by dissolving in dry ether, and recovered by removing the ether from the filtered solution under reduced pressure. It then remained as a colourless solid, m. p. 41—43° (Found: C, 45·5; H, 7·4; Cl, 33·8; *M*, 207. $C_8H_{16}N_2Cl_2$ requires C, 45·5; H, 7·6; Cl, 33·6%; *M*, 211). It could not be distilled unchanged, even under reduced pressure, owing to further polymerisation with the formation of a high-melting solid which dissolved in water and contained chloride ion.

Methyldi-(2-*hydroxyethyl*)*amine*.—(*a*) After di-(2-hydroxyethyl)amine (105 g.) had been carefully neutralised with concentrated hydrochloric acid and the water removed under reduced pressure at 60—70°, paraformaldehyde (50 g.) was added and the mixture heated under reflux in an oil-bath (compare Eschweiler, *Ber.*, 1905, **38**, 880). Evolution of carbon dioxide began when the temperature of the bath reached 140° and continued steadily for 1—1½ hours at 160—165°. After 3 hours at this temperature, the product was cooled, neutralised with solid sodium hydroxide, and distilled. The fraction (92 g.) boiling at 125—135°/14 mm. was redistilled, and methyldi-(2-hydroxyethyl)amine (75 g.; 63% yield) collected at 130°/14 mm. as a colourless oil.

(*b*) Di-(2-hydroxyethyl)amine (52·5 g.) was neutralised with anhydrous formic acid (23 g.) and heated with paraformaldehyde (15 g.) (compare Hanby and Rydon, *J.*, 1947, 513). Evolution of carbon dioxide began at 50°, was torrential at 100—110°, and was practically complete after 10 minutes. At the end of ½ hour, methyldi-(2-hydroxyethyl)amine (55 g.; 92% yield) was isolated by distilling the mixture.

Methyliminodiacetic Acid.—When a mixture of iminodiacetic acid (13·3 g.), formic acid (4·6 g.), aqueous formaldehyde (10 c.c. of 36%), and water (5 c.c.) was heated on a steam-bath, gentle evolution of carbon dioxide ensued. After 2 hours, the whole was boiled under reflux for 10 minutes and then treated with alcohol. The precipitated methyliminodiacetic acid was crystallised from aqueous alcohol (charcoal) and obtained in colourless prisms (12·2 g.), m. p. 223—225° (decomp.) (Found: C, 40·6; H, 6·1. Calc. for $C_5H_9O_4N$: C, 40·8; H, 6·1%).

NNN'N'-*Tetra*-(2-*chloroethyl*)*ethylenediamine*.—The dihydrochloride of *NNN'N'*-tetra-(2-hydroxyethyl)ethylenediamine was obtained as a syrup, which slowly solidified, when the base, prepared by the method of Knorr and Brownsdon (*Ber.*, 1902, **35**, 4470), was dissolved in a slight excess of hydrochloric acid and the solution evaporated under reduced pressure. A suspension of the salt (50 g.) in chloroform (55 c.c.) was treated gradually with a solution of thionyl chloride (92 c.c.) in chloroform (100 c.c.) while the temperature was maintained at 55°, and the whole was then refluxed until the evolution of hydrogen chloride ceased. All volatile material was expelled under reduced pressure at 50°, the residue dissolved in dilute hydrochloric acid, and a small quantity of insoluble oil removed with ether. The basic product was recovered from the aqueous solution by the cautious addition of solid sodium carbonate, and extracted with ether. After the extract had been dried ($MgSO_4$) and evaporated at 50° under reduced pressure, NNN'N'-*tetra*-(2-*chloroethyl*)*ethylenediamine* remained as a brown oil (Found: Cl, 43·4, 42·9. $C_{10}H_{20}N_2Cl_4$ requires Cl, 45·8%). It was not possible to distil this product, since on being heated to 130°/0·02 mm. the whole became solid as a result of quaternary salt formation. This was confirmed by the fact that the solid gave the test for chloride ion when dissolved in water. In fact, salt formation occurred so readily that the oily base became partly solid on being kept for a short time at room temperature.

Tri-(2-*chloroethylthioethyl*)*amine Hydrochloride* [$(CH_2Cl\cdot CH_2\cdot S\cdot CH_2\cdot CH_2)_3N,HCl$].—Tri-(2-chloroethyl)-amine hydrochloride (16·1 g.) and monothioethylene glycol (16 g.) in cold alcohol (180 c.c.) were added to a solution of sodium (6·1 g.) in alcohol (120 c.c.) containing potassium iodide (1 g.). On warming, sodium chloride was rapidly precipitated, and, after heating for ½ hour under reflux, the liquid was filtered and evaporated. The colourless, syrupy residue, a specimen of which decomposed on attempted distillation at 0·05 mm., was dissolved in concentrated hydrochloric acid (150 c.c.), and the solution heated for 2 hours on the steam-bath. The red oil which gradually separated was extracted with chloroform, and the extract dried (Na_2SO_4) and evaporated. The residual syrupy *tri*-(2-*chloroethylthioethyl*)*amine hydrochloride* (15 g.) could not be crystallised (Found: N, 3·2; Cl, 36·9; S, 22·6. $C_{12}H_{25}NCl_4S_3$ requires N, 3·3; Cl, 33·8; S, 22·8%).

2-*Chloro- and* 2-*Bromo*-2′-*phthalimidodiethyl Sulphide*.—Monothioethylene glycol (7·8 g.) and sodium iodide (1 g.) were dissolved in a solution of sodium (2·3 g.) in alcohol (50 c.c.), and the whole treated with phthalo-2-bromoethylimide (25·4 g.) in alcohol (75 c.c.). Sodium bromide was rapidly precipitated, and, after 10 minutes on a steam-bath, the solution was cooled, filtered, and evaporated. The syrupy hydroxy-compound was dissolved in chloroform (25 c.c.) and treated with thionyl chloride (15 g.). After 2 hours, the solution was evaporated under reduced pressure, and when the residue was crystallised from alcohol, 2-chloro-2′-phthalimidodiethyl sulphide (compare Gabriel, *Ber.*, 1891, **24**, 3098) was obtained in colourless needles, m. p. 75—76° (Found: C, 53·3; H, 4·3. Calc. for $C_{12}H_{12}O_2NClS$: C, 53·4; H, 4·5%).

When a solution of the above syrupy hydroxy-compound in hot hydrobromic acid (*d* 1·5) was kept for a few minutes at 100°, an oil separated, and this solidified on cooling. After it had been crystallised from methyl alcohol, 2-bromo-2′-phthalimidodiethyl sulphide (compare Gabriel, *loc. cit.*) was obtained in colourless plates, m. p. 87—88° (Found: C, 46·2; H, 3·9. Calc. for $C_{12}H_{12}O_2NBrS$: C, 45·9; H, 3·8%).

Tri-(2-bromoethyl)amine.—Tri-(2-hydroxyethyl)amine hydrobromide (46 g.), suspended in chloroform (50 c.c.), was treated with phosphorus pentabromide (130 g.), and the reaction completed by heating the mixture under reflux on a water-bath. When cold, the *tri-(2-bromoethyl)amine hydrobromide* (60 g.) was filtered off, washed with chloroform, and crystallised from aqueous acetone, from which it separated in colourless needles, m. p. 153—154° (Found : C, 16·5; H, 3·3. $C_6H_{13}NBr_4$ requires C, 17·2; H, 3·1%). The *base* was liberated as an oil, which rapidly solidified, when a solution of the hydrobromide in the minimum quantity of warm water was treated with the calculated quantity of solid sodium carbonate. When distilled, it was obtained as a colourless liquid, b. p. 145°/0·05 mm., which solidified, and then melted again at 30° (Found : N, 4·1. $C_6H_{12}NBr_3$ requires N, 4·1%).

Dimethyldi-(2-chloroethyl)ammonium Chloride.—After an excess of methyl iodide had been added to a solution of methyldi-(2-chloroethyl)amine in a small amount of benzene, and the whole left for a few hours, the solid methiodide was collected and washed with acetone. It was dissolved in water, and the solution shaken at room temperature for a short time with an excess of freshly precipitated silver chloride. When the solvent was removed from the filtered solution under reduced pressure, and the residue ground with acetone and crystallised from alcohol, *dimethyldi-(2-chloroethyl)ammonium chloride* was obtained in colourless prisms which turned brown and decomposed at 218° (Found : C, 35·2; H, 6·9; Cl, 52·0. $C_6H_{14}NCl_3$ requires C, 34·9; H, 6·8; Cl, 51·6%).

Di-(2-fluoroethyl)amine.—Dry ammonia was passed into a solution of 2-fluoroethyl bromide (100 g., prepared from 2-fluoroethanol and phosphorus tribromide under conditions communicated by Dr. H. McCombie and Dr. B. C. Saunders) in alcohol (400 c.c.) until the weight had increased by 21 g., and the whole was heated for 7 hours in an autoclave at 70°. When cold, it was found that a large amount of solid had separated. Concentrated hydrochloric acid was added until the mixture was acidic, and the alcohol was removed as completely as possible by heating on a water-bath under reduced pressure. After the residue had been made alkaline with a concentrated solution of sodium hydroxide, with cooling, the mixture was submitted to prolonged continuous extraction with ether. The extract was dried ($MgSO_4$), and the solvent removed through a fractionating column. When the residue was distilled from a flask fitted with a short column, *di-(2-fluoroethyl)amine* (10 g.) was collected as a colourless liquid in the form of a well-defined fraction, b. p. 123—126°/764 mm. (Found : N, 12·6; equiv., 111. $C_4H_9NF_2$ requires N, 12·8%; equiv., 109). The base, which is very soluble in water, showed no apparent change on being kept for several weeks.

In the fractionation of the above extract a small quantity of liquid was collected at 35—42°, and when dry hydrogen chloride was passed into it, the hydrochloride of 2-fluoroethylamine (2 g.) was precipitated as a colourless, hygroscopic solid. After it had been recrystallised from alcohol, the salt (1·1 g.) was dissolved in water containing sodium hydroxide (1 g.), and the solution shaken for several hours with toluene-*p*-sulphonyl chloride (1·3 g.) dissolved in ether. When the aqueous layer was acidified with hydrochloric acid, *toluene-*p*-sulphon-2-fluoroethylamide* was precipitated. It was recrystallised from aqueous alcohol and obtained in colourless needles, m. p. 104° (Found : N, 7·0. $C_9H_{12}O_2NFS$ requires N, 6·5%).

N-Phenyl-N'N'-di-(2-fluoroethyl)urea.—Di-(2-fluoroethyl)amine (0·5 g.) was kept cold while phenyl *iso*cyanate (0·5 g.) was gradually added. When the product, which rapidly solidified, was crystallised from benzene–petroleum (b. p. 60—80°), *N-phenyl-N'N'-di-(2-fluoroethyl)urea* separated in colourless needles, m. p. 91° (Found : N, 12·4. $C_{11}H_{14}ON_2F_2$ requires N, 12·3%).

*Toluene-*p*-sulphondi-(2-fluoroethyl)amide.*—A solution of the secondary base (1 g.) in water (20 c.c.) containing sodium hydroxide (0·37 g.) was mechanically shaken for 8 hours with toluene-*p*-sulphonyl chloride (1·74 g.) in ether (18 c.c.). After the ethereal layer had been dried ($MgSO_4$) and evaporated and the residual solid crystallised from petroleum (b. p. 80—100°), *toluene-*p*-sulphondi-(2-fluoroethyl)-amide* was obtained in colourless needles, m. p. 79° (Found : N, 4·8. $C_{11}H_{15}O_2NF_2S$ requires N, 5·3%).

*2-Fluoroethyl Toluene-*p*-sulphonate.*—A mixture of 2-fluoroethanol (150 g.) and toluene-*p*-sulphonyl chloride (180 g.) was refluxed for 10 hours, access of moisture being prevented by a calcium chloride tube. After the excess of 2-fluoroethanol (b. p. 103·5°) had been distilled off, the residue was dissolved in ether, and shaken first with water, then twice with dilute aqueous sodium carbonate, and finally again with water. The ethereal solution was dried ($MgSO_4$), the solvent removed, and the residue distilled under reduced pressure. *2-Fluoroethyl toluene-*p*-sulphonate* (148 g.) was obtained as a colourless oil, b. p. 135—136°/1 mm. (Found : C, 49·7; H, 5·3; F, 8·9. $C_9H_{11}O_3FS$ requires C, 49·5; H, 5·0; F, 8·7%).

Methyldi-(2-fluoroethyl)amine.—Dry methylamine was passed into alcohol until the concentration, found by titration, was 62 g. per litre. A mixture of 2-fluoroethyl toluene-*p*-sulphonate (124 g.) and the alcoholic methylamine (275 c.c.) was heated in pressure bottles in a water-bath at 50—55° for 9 hours. The reaction mixture was treated as described for di-(2-fluoroethyl)amine, and *methyldi-(2-fluoroethyl)-amine* (8·6 g.) was obtained as a colourless liquid, b. p. 123—124°/762 mm. (Found : C, 48·9; H, 9·3; N, 11·8; F, 30·3; equiv., 124. $C_5H_{11}NF_2$ requires C, 48·8; H, 8·9; N, 11·4; F, 30·9%; equiv., 123). The base is very soluble in water, and remained clear on being kept for several days.

Dimethyldi-(2-fluoroethyl)ammonium Iodide.—When the above tertiary base (1 g.) was stirred with methyl iodide (2·5 g.), a solid rapidly separated. After the excess of methyl iodide had been evaporated, the residue was crystallised from acetone, and *dimethyldi-(2-fluoroethyl)ammonium iodide* obtained in colourless prisms, m. p. 200° (decomp.) (Found : I, 47·8. $C_6H_{14}NF_2I$ requires I, 47·9%).

Tri-(2-fluoroethyl)amine.—After di-(2-fluoroethyl)amine (13·6 g.), 2-fluoroethyl bromide (16·0 g.), and alcohol (50 c.c.) had been heated together in a pressure bottle at 70° for 7 hours, the mixture was treated as described for di-(2-fluoroethyl)amine. A considerable quantity (6·7 g.) of unchanged secondary base was collected at 122—125°, and *tri-(2-fluoroethyl)amine* (2 g.) then distilled at 73—74°/25 mm. (Found : N, 9·2; F, 36·7; equiv., 156. $C_6H_{12}NF_3$ requires N, 9·0; F, 36·8%; equiv., 155). The tertiary base is a colourless liquid, and not very soluble in water.

2-Chloroethyldi-(2-fluoroethyl)amine.—Di-(2-fluoroethyl)amine (14 g.) was slowly added with mechanical stirring to a mixture of water (3·5 g.) and ethylene oxide (8·5 g.) cooled to 9° in an apparatus fitted with a reflux condenser which consisted of a coil surrounded by a mixture of ice and salt. After the mixture had been kept at 15—20° for 19 hours, the temperature was raised to 40° for 3 hours and then to 50°

for an hour. The whole was then cooled in a freezing mixture and acidified with concentrated hydrochloric acid. When the solution was evaporated to dryness on a steam-bath under a pressure of 40 mm., the hydrochloride of di-(2-fluoroethyl)-2-hydroxyethylamine remained as a pale yellow, viscous syrup. A solution of thionyl chloride (23 g.) in chloroform (70 c.c.) was gradually added to a mechanically stirred mixture of the above hydrochloride and chloroform (60 c.c.) at 60° in an apparatus fitted with a reflux condenser. After the whole had been kept at 60° for an hour, methyl alcohol (8 c.c.) was added, and all volatile material removed by warming at a pressure of 25 mm. The residual 2-chloroethyldi-(2-fluoroethyl)amine hydrochloride solidified, on cooling, to a deliquescent mass which was dissolved in water (20 c.c.). After the addition of chloroform, the whole was cooled below 0° and mechanically stirred while a solution of potassium hydroxide (7·5 g.) in water (50 c.c.) was gradually added. The chloroform solution was dried and the solvent removed through a short column under reduced pressure. When the residue was distilled, *2-chloroethyldi-(2-fluoroethyl)amine* (9·4 g.) was collected as a colourless liquid, b. p. 95—97°/19 mm. (Found: N, 8·2; Cl, 20·8; F, 21·8. $C_6H_{12}NClF_2$ requires N, 8·2; Cl, 20·7; F, 22·2%). The base is not very soluble in water and is comparatively stable; only a trace of solid had separated after a fortnight.

When the base was treated with an equivalent amount of picric acid in dry benzene, the *picrate* quickly separated. It was recrystallised from alcohol and obtained in yellow needles, m. p. 121° (Found: C, 36·2; H, 3·8; Cl, 8·8. $C_{12}H_{13}O_7N_4ClF_2$ requires C, 36·0; H, 3·7; Cl, 8·9%).

Di-(2-chloroethyl)-2-fluoroethylamine.—A mixture of potassium phthalimide (160 g.) and 2-fluoroethyl bromide (180 g.) was heated at 180—190° for 8 hours in sealed tubes, and the product heated and stirred for an hour with water (800 c.c.) on a steam-bath. The mixture was cooled to the point at which the crude alkylphthalimide solidified, and rapidly filtered. After the solid had been ground with cold methyl alcohol (120 c.c.), it was further purified by dissolving it in chloroform (400 c.c.) at room temperature, filtering the solution from a small amount of insoluble material, and removing the solvent. When the residue was crystallised from alcohol, *phthalo-2-fluoroethylimide* (132 g.) was obtained in long, fawn-coloured needles, m. p. 100° (Found: C, 62·5; H, 4·2. $C_{10}H_8O_2NF$ requires C, 62·2; H, 4·1%). After a solution of this substance (63·6 g.) in alcohol (200 c.c.) had been treated with hydrazine hydrate (16·5 g.) and boiled under reflux for ½ hour, the whole was acidified with concentrated hydrochloric acid, and boiling was continued for an hour (compare Ing and Manske, *J.*, 1926, 2348). When cold, the mixture was filtered, the solid washed twice with water, and the combined filtrate and washings were evaporated to dryness under reduced pressure. A filtered solution of the residue in water (100 c.c.) was shaken for 2½ hours with salicyl aldehyde (40 c.c.) to remove hydrazine, and all insoluble material extracted with ether. When the aqueous liquid was again evaporated to dryness, 2-fluoroethylamine hydrochloride (23·8 g.) remained as a brown syrup which set to a deliquescent glassy solid (compare Traube and Peiser, *Ber.*, 1920, **53**, 1501). Its composition was confirmed by converting a little of it into toluene-*p*-sulphon-2-fluoroethylamide, identical with the substance described above. A solution of this hydrochloride (48 g.) in water (125 c.c.) was treated with aqueous potassium hydroxide (288 c.c. of 1·68N) and then gradually added with mechanical stirring to ethylene oxide (100 g.) at 9—11° under a reflux condenser which was surrounded by a mixture of ice and salt. After stirring had been continued for 3 hours at this temperature, the whole was left overnight. The isolation of the hydrochloride of the dihydroxy-compound and its conversion into *di-(2-chloroethyl)-2-fluoroethylamine* followed along lines similar to those described for 2-chloroethyldi-(2-fluoroethyl)amine. The product (12·7 g.) was collected as an almost colourless liquid, b. p. 115°/13 mm. (Found: C, 38·5; H, 6·5; Cl, 38·1. $C_6H_{12}NCl_2F$ requires C, 38·3; H, 6·4; Cl, 37·8%). The base is not very soluble in water and is comparatively stable. It remained clear for several days, but a specimen which was kept for 5 weeks deposited a small amount of white solid and a few drops of a dark brown, gummy material.

We are indebted to Sir Robert Robinson for his interest in these investigations, and to the Chief Scientist, Ministry of Supply, for permission to publish the work.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, February 20th*, 1948.]

---

440. *Some Sulphides containing the 2-Chloroethyl Group.*

By L. J. GOLDSWORTHY, G. F. HARDING, W. L. NORRIS, S. G. P. PLANT, and B. SELTON.

The preparation of several compounds belonging to the types R·S·CH_2·CH_2Cl, R·O·CH_2·CH_2·S·CH_2·CH_2Cl, and R·S·CH_2·CH_2·S·CH_2·CH_2Cl has been investigated on account of the possible interest attaching to these substances as vesicants. Some of the sulphides have been converted into sulphones and sulphilimines.

As part of an investigation designed to compare the vesicant properties of a series of compounds containing the ·S·CH_2·CH_2Cl group, several sulphides of this type not hitherto recorded have been prepared.

The reactions used by Demuth and Meyer (*Annalen*, 1887, **240**, 305) to obtain 2-chlorodiethyl sulphide, and represented by the scheme Et·SH ⟶ Et·S·CH_2·CH_2·OH ⟶ Et·S·CH_2·CH_2Cl, can be employed for other 2-chloroethyl alkyl sulphides (see, *e.g.*, Dawson, *J. Amer. Chem. Soc.*, 1933, **55**, 2070), and have now been applied to the preparation of *2-chloroethyl* n-*heptyl*, n-*nonyl*, and n-*undecyl sulphides*.

Four 2-alkoxyethylthiols, R·O·CH_2·CH_2·SH (R = Me, Et, *n*-Pr, and *n*-Bu), have been obtained from the appropriate 2-alkoxyethyl halides, and converted by a similar series of reactions into 2-*chloro*-2′-*methoxydiethyl sulphide*, Me·O·CH_2·CH_2·S·CH_2·CH_2Cl, and the analogous ethoxy-, n-*propoxy*-, and n-*butoxy*-compounds. The corresponding 2-alkylthioethylthiols, R·S·CH_2·CH_2·SH (R = Me, Et, *n*-Pr, and *n*-Bu), obtained from the 2-chloroethyl alkyl sulphides, were transformed by similar stages into 2-chloro-2′-methylthiodiethyl sulphide, Me·S·CH_2·CH_2·S·CH_2·CH_2Cl, and its ethyl, n-*propyl*, and n-*butyl* analogues.

2-*Chlorodiethyl sulphone*, 2-*chloro*-2′-n-*propoxydiethyl sulphone*, and 2-*chloro*-2′-n-*butylsulphonyldiethyl sulphone*, C_4H_9·SO_2·CH_2·CH_2·SO_2·CH_2·CH_2Cl, have been prepared from the sulphides, the conversion of some of which into sulphilimines has been studied. In this connexion, while methyl 2-chloroethyl sulphide, 2-chloroethyl allyl sulphide, 2-chloro-2′-methoxydiethyl sulphide, and 2-chloro-2′-*n*-propoxydiethyl sulphide readily gave crystalline *sulphilimines* on shaking with an aqueous solution of chloramine-T, homogeneous products were not obtained from 2-chloroethyl *n*-undecyl sulphide, 2-chloro-2′-ethoxydiethyl sulphide, the corresponding *n*-butoxy-compound, and 2-chloro-2′-*n*-propylthiodiethyl sulphide, and pure substances were not obtained on recrystallisation, except from the last-named which yielded toluene-*p*-sulphonamide. The remarkable difference in the ease with which this reaction ensues with these closely related sulphides is not without parallel, for although 2 : 2′-dichlorodiethyl sulphide readily gives a sulphilimine (Mann and Pope, *J.*, 1922, **121**, 1052), yet Davies and Oxford (*J.*, 1931, 224) obtained toluene-*p*-sulphonamide as the only pure product from 1 : 2′-dichlorodiethyl sulphide and chloramine-T.

Experimental.

2-*Chloroethyl Alkyl Sulphides*.—After *n*-heptylthiol (44 g.) had been dissolved in a solution of sodium (7·7 g.) in alcohol (130 c.c.), ethylene chlorohydrin (27 g.) was gradually added with shaking and cooling. The mixture was then heated for ½ hour on a steam-bath, and, when cold, the precipitate of sodium chloride was removed by filtration and washed with a little alcohol. The solvent was removed from the united alcoholic solutions by distillation and the residual oil was decanted from a further small quantity of sodium chloride. It was then distilled under reduced pressure, and 2-hydroxyethyl *n*-heptyl sulphide was collected at 153—154°/33 mm. in good yield. Thionyl chloride (26·5 g.) in chloroform (60 c.c.) was gradually added with shaking to the hydroxy-compound (35 g.) in chloroform (30 c.c.), the temperature being maintained at about 40° until the evolution of gas had slackened. The mixture was then kept at 60° to effect completion of the reaction, and the solvent and excess of thionyl chloride were removed by distillation from a steam-bath. When the residual oil was fractionated, 2-*chloroethyl* n-*heptyl sulphide* was obtained as a colourless oil, b. p. 139—140°/25 mm. (Found : Cl, 17·8; S, 16·4. $C_9H_{19}ClS$ requires Cl, 18·3; S, 16·5%).

The following were similarly prepared : 2-*chloroethyl* n-*nonyl sulphide*, colourless oil, b. p. 164—166°/20 mm. (Found : Cl, 15·4. $C_{11}H_{23}ClS$ requires Cl, 15·9%), *via* 2-hydroxyethyl *n*-nonyl sulphide, b. p. 174—176°/20 mm.; 2-*hydroxyethyl* n-*undecyl sulphide*, m. p. 26—27°, b. p. 185—186°/15 mm. (Found : C, 66·9; H, 12·1. $C_{13}H_{28}OS$ requires C, 67·2; H, 12·1%); 2-*chloroethyl* n-*undecyl sulphide*, colourless oil, b. p. 175—179°/14 mm. (Found : C, 62·4; H, 10·9; Cl, 14·3. $C_{13}H_{27}ClS$ requires C, 62·3; H, 10·8; Cl, 14·2%); 2-chlorodiethyl sulphide, b. p. 154—155° (compare Demuth and Meyer, *loc. cit.*); 2-chloroethyl *n*-propyl sulphide, b. p. 74—75°/22 mm. (compare Dawson, *loc. cit.*); 2-chloroethyl *n*-butyl sulphide, b. p. 89°/20 mm. (compare Whitner and Reid, *J. Amer. Chem. Soc.*, 1921, **43**, 636; Dawson, *loc. cit.*); 2-chloroethyl benzyl sulphide, b. p. 137—138°/12 mm. (Found : Cl, 19·1. Calc. for $C_9H_{11}ClS$: Cl, 19·0%) (compare Dawson, *loc. cit.*).

2-*Chloro*-2′-*alkoxydiethyl Sulphides*.—The 2-alkoxyethanols, R·O·CH_2·CH_2OH (R = Me, *n*-Pr, and *n*-Bu), were prepared by the methods of Cretcher and Pittenger (*J. Amer. Chem. Soc.*, 1924, **46**, 1503) and converted into the corresponding bromides as described by Palomaa and Kenetti (*Ber.*, 1931, **64**, 797), and 2-ethoxyethyl chloride was made from ethylene chlorohydrin by the method of Swallen and Boord (*J. Amer. Chem. Soc.*, 1930, **52**, 651).

2-Methoxyethyl bromide (99 g.) was added to a solution of potassium hydrogen sulphide made by saturating potassium hydroxide (80 g.) in methyl alcohol (300 c.c.) with hydrogen sulphide. After the mixture had been quickly shaken, it was placed in a pressure bottle and left overnight. The thiol, b. p. 109—110°, was isolated by diluting the mixture with water, extracting with light petroleum, and fractionating the dried extract. The yield (9 g.; 14%) was poor, and since there was only a small quantity of the corresponding sulphide in the form of higher-boiling material, it seems probable that a considerable amount of the original bromide was transformed into methyl vinyl ether. The theoretical quantity of ethylene chlorohydrin was added to a solution of the thiol in alcohol containing slightly more than one molecular proportion of sodium ethoxide. After the whole had been refluxed for an hour, it was cooled, and the sodium chloride removed by filtration. When the alcohol was removed from the filtrate and the residue fractionated, 2-hydroxy-2′-methoxydiethyl sulphide was obtained as a colourless oil, b. p. 112°/15 mm. (Found : C, 43·4; H, 8·4. Calc. for $C_5H_{12}O_2S$: C, 44·1; H, 8·8%). This compound has been isolated by Kretov (*J. Russ. Phys. Chem. Soc.*, 1929, **61**, 2345) from the products of the action of zinc on 2 : 2′-dichlorodiethyl sulphide in the presence of methyl alcohol. The process used to replace hydroxyl by chlorine in the substance was similar to that described above for the preparation of 2-chloroethyl *n*-heptyl sulphide, and 2-*chloro*-2′-*methoxydiethyl sulphide* was obtained as a colourless oil, b. p. 88°/12 mm. (Found : Cl, 23·0. $C_5H_{11}OClS$ requires Cl, 23·0%).

2-*Chloro*-2′-n-*propoxydiethyl sulphide*, colourless oil, b. p. 109—110°/12 mm. (Found : Cl, 19·6.

$C_7H_{15}OClS$ requires Cl, 19·5%), was similarly prepared *via* 2-*n*-propoxyethylthiol, b. p. 48—50°/17 mm. (yield 65%), and 2-hydroxy-2′-*n*-propoxydiethyl sulphide, b. p. 128—129°/12 mm. *2-Chloro-2′-n-butoxydiethyl sulphide*, colourless oil, b. p. 124°/12 mm. (Found: Cl, 17·7. $C_8H_{17}OClS$ requires Cl, 18·1%), was also similarly obtained *via* 2-*n*-butoxyethylthiol, b. p. 167° (yield: 68%), and 2-hydroxy-2′-*n*-butoxydiethyl sulphide, b. p. 141°/15 mm.

2-Ethoxyethylthiol was prepared from 2-ethoxyethyl chloride by the method of Swallen and Boord (*loc. cit.*) and converted by a process similar to that described above for the methoxy-compound into 2-hydroxy-2′-ethoxydiethyl sulphide, b. p. 115—117°/13 mm., which has been obtained in small amounts from 2 : 2′-dichlorodiethyl sulphide by Kretov (*loc. cit.*) by the action of zinc in the presence of alcohol, and by Davies and Oxford (*loc. cit.*) by hydrolysis with aqueous-alcoholic potassium hydroxide. The hydroxy-compound (158 g.) in dimethylaniline (191 g.) was kept cold while thionyl chloride (188 g.) was gradually added. After a short time the mixture was heated for 15 minutes on a steam-bath and then poured into an excess of dilute hydrochloric acid. The product was extracted with chloroform, dried ($CaCl_2$), and fractionated. 2-Chloro-2′-ethoxydiethyl sulphide was obtained as a colourless oil (147 g.), b. p. 92·5°/11 mm. (Found: C, 42·9; H, 7·5; Cl, 20·6. Calc. for $C_6H_{13}OClS$: C, 42·7; H, 7·7; Cl, 21·1%) (compare Kretov, *loc. cit.*).

2-Chloro-2′-alkylthiodiethyl Sulphides.—A solution of sodium (1·1 mols.) in alcohol was saturated with hydrogen sulphide at 0°, mixed with methyl 2-chloroethyl sulphide (prepared as described in *Org. Synth.*, **14**, 18), and heated in a pressure bottle at 60—65° for 6 hours. 2-Methylthioethylthiol, b. p. 57—61°/15 mm. (compare Moggridge, *J.*, 1946, 1105), was isolated by pouring the mixture into water, and purified by distillation. The thiol was dissolved in an alcoholic solution of sodium ethoxide (1·05 mols.), and the whole raised to boiling with stirring under reflux on a water-bath. The flame was removed while ethylene chlorohydrin (1·1 mols.) was gradually added during ½—1 hour with continued stirring. After the sodium chloride had been filtered off, the alcohol was removed on a steam-bath and the residue distilled under reduced pressure. 2-Hydroxy-2′-methylthiodiethyl sulphide was collected at 139—140°/9·5 mm. (compare Brown and Moggridge, *J.*, 1946, 816, who made this substance from monothioethylene glycol). A solution of the hydroxy-compound in twice its volume of chloroform was boiled under reflux in an all-glass apparatus (the use of corks led to a dark brown material, the purification of which was difficult), and the flame was removed while thionyl chloride (1·1 mols.) in four times its volume of chloroform was fairly rapidly added down the condenser. The whole was refluxed until hydrogen chloride was no longer evolved (1½—3 hours). When all volatile material had been removed on the steam-bath, finally under reduced pressure, 2-chloro-2′-methylthiodiethyl sulphide (compare Brown and Moggridge, *loc. cit.*) remained as a colourless oil, which solidified on being cooled and then melted again between 7° and 13° (Found: C, 35·2; H, 6·7; Cl, 19·4. Calc. for $C_5H_{11}ClS_2$: C, 35·2; H, 6·5; Cl, 20·8%).

2-Chloro-2′-ethylthiodiethyl sulphide (Found: C, 38·1; H, 7·0; Cl, 18·8. Calc. for $C_6H_{13}ClS_2$: C, 39·0; H, 7·0; Cl, 19·2%), similarly prepared, was obtained as a pale yellow oil which solidified in a freezing mixture and then melted between 4° and 10° (compare Demuth and Meyer, *loc. cit.*). *2-Chloro-2′-n-propylthiodiethyl sulphide* (Found: C, 42·1; H, 7·8; Cl, 17·8. $C_7H_{15}ClS_2$ requires C, 42·3; H, 7·6; Cl, 17·9%) was obtained as a pale yellow oil, which solidified on being cooled and then melted between 1° and 7°, by a similar process *via* 2-*n*-propylthioethylthiol, b. p. 75—77°/11 mm., and 2-hydroxy-2′-*n*-propylthiodiethyl sulphide, b. p. 151—154°/10 mm. *2-Chloro-2′-n-butylthiodiethyl sulphide* (Found: C, 44·9; H, 7·7; Cl, 15·9. $C_8H_{17}ClS_2$ requires C, 45·2; H, 8·0; Cl, 16·7%), a colourless oil which solidified in a freezing mixture and melted again between −8° and −2°, was similarly obtained *via* 2-*n*-butylthioethylthiol b. p. 90—92°/10 mm., and 2-hydroxy-2′-*n*-butylthiodiethyl sulphide, b. p. 163—165°/10 mm. It was not possible satisfactorily to distil any of these four chloro-compounds, owing to the ease with which they decomposed to give 1 : 4-dithian and the corresponding alkyl chloride.

Sulphones.—The following were prepared from the corresponding sulphides by a process similar to that used by Brown and Moggridge (*loc. cit.*) for methyl 2-chloroethyl sulphone: *2-chlorodiethyl sulphone*, b. p. 154—155°/18 mm., m. p. 20° (Found: Cl, 22·4. $C_4H_9O_2ClS$ requires Cl, 22·7%), *2-chloro-2′-n-propoxydiethyl sulphone*, pale yellow oil, b. p. 165—167°/9 mm. (Found: Cl, 16·7. $C_7H_{15}O_3ClS$ requires Cl, 16·6%), and *2-chloro-2′-n-butylsulphonyldiethyl sulphone*. The last was not distilled, but was purified by crystallisation from glacial acetic acid, from which it separated in colourless plates, m. p. 188—189° (Found: Cl, 12·6. $C_8H_{17}O_4ClS_2$ requires Cl, 12·8%).

Sulphilimines.—The *sulphilimines* now described were prepared by shaking the corresponding sulphide with an aqueous solution of chloramine-T (10% excess) until the product had solidified, and were purified by crystallisation from alcohol. That of methyl 2-chloroethyl sulphide was obtained in colourless prisms, m. p. 121° (Found: Cl, 12·7. $C_{10}H_{14}O_2NClS_2$ requires Cl, 12·7%), that of 2-chloroethyl allyl sulphide (the thio-ether was prepared as described by Scherlin and Wasilewsky, *J. pr. Chem.*, 1929, **121**, 173) in colourless prisms, m. p. 60—61° (Found: Cl, 11·6. $C_{12}H_{18}O_2NClS_2$ requires Cl, 11·6%), that of 2-chloro-2′-methoxydiethyl sulphide in colourless needles, m. p. 113° (Found: Cl, 11·1. $C_{12}H_{18}O_2NClS_2$ requires Cl, 11·0%), and that of 2-chloro-2′-*n*-propoxydiethyl sulphide in colourless prisms, m. p. 77—78° (Found: Cl, 10·3. $C_{14}H_{22}O_2NClS_2$ requires Cl, 10·1%).

We are indebted to Sir Robert Robinson for his interest in these investigations, and to the Chief Scientist, Ministry of Supply, for permission to publish the work.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, February 20th*, 1948.]

441. *Compounds containing the 3-Chloroallyl Group.*

By A. F. Childs, S. G. P. Plant, A. L. L. Tompsett, and G. A. Weeks.

As part of an investigation of vesicant compounds and in view of reports that 3-chloroallyl alcohol has a powerful effect on the skin, several substances containing the 3-chloroallyl group have been prepared for examination. These include a number which are analogous to well-known 2-chloroethyl compounds and contain the group attached to sulphur or nitrogen. Some substances containing the 3-chloroallyl group attached to oxygen in esters, urethanes, and acetals have been made, and *3-chloroallyldichloroarsine* has been included.

Several authors have emphasised the vesicant properties of 3-chloroallyl alcohol, $CHCl{:}CH{\cdot}CH_2{\cdot}OH$ (van Romburgh, *Bull. Soc. chim.*, 1881, **36**, 555; Henry, *Compt. rend.*, 1882, **95**, 851; Kirrmann, Pacaud, and Dosque, *Bull. Soc. chim.*, 1934, **1**, 860). As part of an investigation into vesicant substances, it appeared of importance therefore to prepare certain compounds containing the 3-chloroallyl group, and related to known toxic types. For this purpose 3-chloroallyl chloride $CHCl{:}CH{\cdot}CH_2Cl$, was obtained by dehydraton of glycerol 1 : 3-dichlorohydrin, $CH_2Cl{\cdot}CH(OH){\cdot}CH_2Cl$, with phosphorus oxychloride as described by Hill and Fischer (*J. Amer. Chem. Soc.*, 1922, **44**, 2582). When treated with alcoholic sodium sulphide, the chloride gave 3 : 3′-*dichlorodiallyl sulphide*, $(CHCl{:}CH{\cdot}CH_2)_2S$, while 2-*hydroxyethyl* 3-*chloroallyl sulphide*, $CH_2(OH){\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH{:}CHCl$, was obtained by the action of the sodium salt of monothioethylene glycol. This hydroxy-compound, which was also prepared from the thiol, $CHCl{:}CH{\cdot}CH_2{\cdot}SH$, and ethylene chlorohydrin, was converted by thionyl chloride into 2-*chloroethyl* 3-*chloroallyl sulphide*, $CH_2Cl{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH{:}CHCl$, whence by a similar sequence of reactions with monothioethylene glycol 1-(2′-*hydroxyethylthio*)- and 1-(2′-*chloroethylthio*)-2-(3′-*chloroallylthio*)*ethane*, $CH_2R{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH{:}CHCl$ (R = OH or Cl), were obtained. 1 : 2-*Di*-(3′-*chloroallylthio*)*ethane*, $(CHCl{:}CH{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot})_2$, was prepared from the above thiol and ethylene dibromide, and *methyl* 3-*chloroallyl sulphide*, $CH_3{\cdot}S{\cdot}CH_2{\cdot}CH{:}CHCl$, from the chloride and methylthiol.

Di-(3-*chloroallyl*)*amine*, $(CHCl{:}CH{\cdot}CH_2)_2NH$, and *tri*-(3-*chloroallyl*)*amine*, $(CHCl{:}CH{\cdot}CH_2)_3N$, have been isolated from the product of the action of alcoholic ammonia on 3-chloroallyl chloride, while the tertiary base has also been obtained in a similar way from the corresponding iodide. The secondary base was methylated by heating its formate with paraformaldehyde (compare Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571; see also this vol., p. 2174) with the formation of methyldi-(3-chloroallyl)amine, which has been described by von Braun, Kühn, and Weismantel (*Annalen*, 1926 **449**, 249) as one of the products of the action of methylamine on 3-chloroallyl chloride.

Several substances containing the 3-chloroallyl group attached to oxygen have been prepared. The action of silver chloroacetate on 3-chloroallyl iodide gave the expected *ester*, from which 3-*chloroallyl iodoacetate*, $CH_2I{\cdot}CO_2CH_2{\cdot}CH{:}CHCl$, was obtained by treatment with sodium iodide in acetone. Addition of 3-chloroallyl alcohol to carbonyl chloride led to the *chloroformate*, $Cl{\cdot}CO_2CH_2{\cdot}CH{:}CHCl$, which was converted by aniline into 3-*chloroallyl carbanilate*, $NHPh{\cdot}CO_2CH_2{\cdot}CH{:}CHCl$, also obtained from the alcohol and phenyl *iso*cyanate, and by 2-chloroethylamine into the corresponding 2-*chloroethylcarbamate*, $CH_2Cl{\cdot}CH_2{\cdot}NH{\cdot}CO_2CH_2{\cdot}CH{:}CHCl$. Attempts to obtain a nitrosourethane from the latter gave products which could not be purified. Condensation of 3-chloroallyl alcohol with the appropriate aldehydes gave the *acetals*, $CHR(O{\cdot}CH_2{\cdot}CH{:}CHCl)_2$ (R = H or CH_3), while the sulphur-containing *analogue*, $CH_3{\cdot}CH(S{\cdot}CH_2{\cdot}CH{:}CHCl)_2$, was obtained from the corresponding thiol.

3-*Chloroallyl thiocyanate* was prepared from the chloride with potassium thiocyanate, and its identity was confirmed by its conversion into 3-*chloroallyl acetyldithiocarbamate*, $CHCl{:}CH{\cdot}CH_2{\cdot}S{\cdot}CS{\cdot}NHAc$, on treatment with ethanethioic acid (see Wheeler and Merriam, *J. Amer. Chem. Soc.*, 1901, **23**, 283), but when heated in attempts to obtain a mustard oil, it suffered profound decomposition. 3-*Chloroallyldichloroarsine*, $CHCl{:}CH{\cdot}CH_2AsCl_2$, has been made from the chloride through the corresponding arsonic acid.

The presence of the 3-chloroallyl group in a compound leads to the possibility of geometrical isomerism, and frequent reference to this feature was made by us in 1943—1944 in Extra-Mural Reports of the Ministry of Supply. In this connexion it is of interest that Hatch and Moore (*J. Amer. Chem. Soc.*, 1944, **66**, 285) have isolated two forms of 3-chloroallyl chloride, b. p.s 104·3° and 112°, by careful fractionation of a residue obtained from the distillation of crude allyl chloride prepared by the chlorination of propylene, and have converted them into the corresponding forms of 3-chloroallyl alcohol, both of which have delayed vesicant action.

Experimental.

The preparation of 3-chloroallyl chloride by the method of Hill and Fischer (*loc. cit.*) was carried out several times, but the yield of material, b. p. 106—109·5°, never exceeded 40% of the theoretical. Hill and Fischer claim a 75% yield, but Hurd and Webb (*J. Amer. Chem. Soc.*, 1936, **58**, 2190) reported only 34%.

3 : 3′-*Dichlorodiallyl Sulphide.*—When 3-chloroallyl chloride (22·2 g.) was slowly added to a solution of sodium sulphide crystals (24 g.) in hot alcohol (100 c.c.) under reflux, the mixture boiled without external heating. The whole was boiled for a further ½ hour, and most of the alcohol was removed by distillation. The oil which separated when the residue was poured into water was extracted with ether, washed with aqueous sodium hydroxide, and dried. After removal of the ether, the product was distilled and 3 : 3′-*dichlorodiallyl sulphide* (14·9 g.) collected as an almost colourless liquid, b. p. 116—117°/19 mm. (Found : C, 39·0; H, 4·5. $C_6H_8Cl_2S$ requires C, 39·3; H, 4·4%).

2-*Hydroxyethyl* 3-*Chloroallyl Sulphide.*—(A) Monothioethylene glycol (24·6 g.) was added to a solution of sodium (8·3 g.) in alcohol (150 c.c.), the mixture heated to boiling on a water-bath, and the flame removed while 3-chloroallyl chloride (35 g.) was slowly added with mechanical stirring. After the whole had been stirred for a further hour, the sodium chloride was filtered off and washed with alcohol. When the united alcoholic solutions were fractionated, 2-*hydroxyethyl* 3-*chloroallyl sulphide* (34·2 g.) was obtained as a colourless oil, b. p. 136—139°/20 mm. (Found : C, 39·2; H, 6·1. C_5H_9OClS requires C, 39·3; H, 5·9%).

(B) After a solution of sodium (6·9 g.) in alcohol (120 c.c.) had been saturated with dry hydrogen sulphide at 0°, 3-chloroallyl chloride (27·7 g.) was added, and the mixture heated in pressure bottles at 60° for 6 hours. The oily thiol which separated when the whole was poured into water was extracted with ether, dried, and distilled. It was obtained as a colourless liquid (12·2 g.), b. p. 43—45°/27 mm., and was then added to a solution of sodium (3 g.) in alcohol (65 c.c.). After the mixture had been heated to the boiling point, ethylene chlorohydrin (10·4 g.) was added during 40 minutes with mechanical stirring, the whole was refluxed for ½ hour, the sodium chloride removed by filtration, and the alcoholic solution fractionated. 2-Hydroxyethyl 3-chloroallyl sulphide (7·9 g.) was collected at 135—137·5°/16 mm. (Found : C, 38·7; H, 5·8%).

2-*Chloroethyl* 3-*Chloroallyl Sulphide.*—Thionyl chloride (16·4 g.) in chloroform (20 c.c.) was slowly added with mechanical stirring to a solution of the above hydroxy-compound (20 g.) in hot chloroform (30 c.c.), and the whole was gently refluxed for 2 hours. When the solution was then fractionated, 2-*chloroethyl* 3-*chloroallyl sulphide* (18·6 g.) was obtained as a colourless oil, b. p. 113—114°/17 mm. (Found : C, 35·2; H, 4·5. $C_5H_8Cl_2S$ requires C, 35·1; H, 4·7%).

1 : 2-*Di*-(3′-*chloroallylthio*)*ethane.*—After the above thiol (21·5 g.), from 3-chloroallyl chloride, had been added to sodium (4·6 g.) in alcohol (150 c.c.), and the whole raised to the boiling point under reflux, ethylene dibromide (19 g.) was added during ½ hour with stirring. When the mixture had been refluxed for 5 hours with continued stirring, and cooled, the sodium bromide was filtered off, and the filtrate fractionated. 1 : 2-*Di*-(3′-*chloroallylthio*)*ethane* (8·1 g.) was collected as a yellow oil, b. p. 192—194°/19 mm., which solidified on standing. After redistillation, the product was crystallised from alcohol and obtained in colourless plates, m. p. 45—49° (Found : C, 39·3; H, 4·8. $C_8H_{12}Cl_2S_2$ requires C, 39·5; H, 4·9%).

1-(2′-*Chloroethylthio*)-2-(3′-*chloroallylthio*)*ethane.*—Obtained from 2-chloroethyl 3-chloroallyl sulphide by a process similar to the first method described above for the preparation of 2-hydroxyethyl 3-chloroallyl sulphide, 1-(2′-*hydroxyethylthio*)-2-(3′-*chloroallylthio*)*ethane* was isolated as a pale brown oil, b. p. 195—200°/27 mm. (Found : C, 39·3; H, 6·1. $C_7H_{12}OClS_2$ requires C, 39·5; H, 6·1%). After its solution in chloroform had been refluxed for an hour in an all-glass apparatus with a small excess of thionyl chloride, all volatile material was removed under reduced pressure at 40°, and 1-(2′-*chloroethylthio*)-2-(3′-*chloroallylthio*)*ethane* remained as a dark brown oil (Found : C, 36·8; H, 5·5. $C_7H_{12}Cl_2S_2$ requires C, 36·4; H, 5·2%). No attempt was made to distil the product since substances of this type readily change into derivatives of 1 : 4-dithian.

Methyl 3-*Chloroallyl Sulphide.*—Prepared from 3-chloroallyl chloride and the sodium salt of methylthiol under conditions similar to those used for 2-hydroxyethyl 3-chloroallyl sulphide (method A), this *sulphide* was obtained as a colourless oil, b. p. 55°/21 mm. (Found : C, 39·0; H, 6·0. C_4H_7ClS requires C, 39·2; H, 5·7%).

Di- and Tri-(3-*chloroallyl*)*amine.*—(A) When dry ammonia was passed into 3-chloroallyl chloride (96 g.), dissolved in alcohol (600 c.c.), until the solution had gained 25 g. in weight, and the whole left for a fortnight at room temperature, a considerable quantity of ammonium chloride separated. After filtration, the filtrate was evaporated to dryness under reduced pressure on a steam-bath, and the residue made alkaline with the least possible quantity of concentrated aqueous potassium hydroxide. The oily product was extracted with ether, and the extract was dried ($MgSO_4$) and fractionated. Three fractions were collected at (i) 40—70°/21 mm., (ii) 105—115°/21 mm., and (iii) 157—159°/21 mm. When the first of these was redistilled at atmospheric pressure, a liquid (3·5 g.), b. p. 95—119°, was collected, and this appeared to consist largely of 3-chloroallylamine, but the primary base has not been obtained in a pure condition. Further distillation of the middle fraction gave *di*-(3-*chloroallyl*)*amine* (9·7 g.) as a pale yellow oil, b. p. 103·5—104°/17 mm. (Found : C, 43·3; H, 5·7; N, 8·5. $C_6H_9NCl_2$ requires C, 43·4; H, 5·4; N, 8·4%). The third fraction (23 g.) was *tri*-(3-*chloroallyl*)*amine*, and on redistillation it was collected as an almost colourless oil at 145—147°/15 mm. (Found : C, 44·5; H, 5·3; N, 6·1. $C_9H_{12}NCl_3$ requires C, 44·9; H, 5·0; N, 5·8%).

(B) When 3-chloroallyl chloride (77·8 g.) was added to a solution of sodium iodide (116 g.) in acetone (600 c.c.), there was an immediate precipitation of sodium chloride. After the whole had been refluxed for 2 hours, some of the acetone (300 c.c.) was distilled off, and the residue treated with water (600 c.c.). When the oily 3-chloroallyl iodide was shaken with aqueous sodium thiosulphate until colourless, dried, and distilled (yield 104·6 g.), it boiled at 69—70°/32 mm. This iodide has been obtained by the use of other reactions (van Romburgh, *Rec. Trav. chim.*, 1882, **1**, 233; Kirrmann, Pacaud, and Dosque, *loc.*

cit.; Bert and Andor, *Compt. rend.*, 1932, **194**, 722). Dry ammonia was passed into a solution of the iodide (100 g.) in alcohol (200 c.c.), cooled in ice-water, until an increase in weight of 14 g. had been attained, and the whole was heated at 60° for 8 hours. When the alcohol was distilled off under reduced pressure and the residue treated as described under (A), tri-(3-chloroallyl)amine (24·5 g.) was obtained at 154—155·5°/17 mm., and the amounts of the lower-boiling fractions were less than from 3-chloroallyl chloride.

Methyldi-(3-chloroallyl)amine.—When a mixture of di-(3-chloroallyl)amine (9·5 g.), anhydrous formic acid (2·65 g.), and paraformaldehyde (1·7 g.) was slowly heated under reflux, the evolution of carbon dioxide began at about 60° and was exceedingly brisk for a few moments. After being kept at 100—120° for ½ hour, the liquid, in ether (50 c.c.), was shaken with toluene-*p*-sulphonyl chloride (1·5 g.) and potassium hydroxide (2 g.), in water (15 c.c.), to ensure removal of any secondary base, the ether washed with water, and the tertiary base extracted with dilute hydrochloric acid. Methyldi-(3-chloroallyl)amine, recovered by the addition of alkali, was extracted with ether, dried, and distilled, and was collected as a colourless oil (7·0 g.), b. p. 95—97°/10 mm. (Found: C, 47·3; H, 6·2. Calc. for $C_7H_{11}NCl_2$: C, 46·7; H, 6·1%).

3-Chloroallyl Chloro- and Iodo-acetate.—When a suspension of dry, freshly prepared silver chloroacetate (85·5 g.) in ether (50 c.c.) was treated with a solution of 3-chloroallyl iodide (45·3 g.) in ether (50 c.c.) under reflux, a steady reaction ensued, the ether boiled without external heating, and the solid became yellow. After the reaction had subsided, the whole was refluxed for 2 hours, cooled, and filtered. The filtrate was fractionated, and *3-chloroallyl chloroacetate* obtained as a colourless oil (17 g.), b. p. 95—100·5°/13 mm. (Found: C, 35·1; H, 3·6. $C_5H_6O_2Cl_2$ requires C, 35·5; H, 3·6%). A mixture of the ester (16·2 g.), sodium iodide (16·2 g.), and acetone (100 c.c.) was refluxed for 2 hours, and filtered from the precipitated sodium chloride. After the precipitate had been washed with acetone, the solvent was distilled from the united solutions, and the residue treated with water. An ethereal extract of the product was shaken with aqueous sodium thiosulphate, dried, and fractionated. *3-Chloroallyl iodoacetate* was collected as a colourless oil (14·4 g.), b. p. 122—124°/14 mm. (Found: C, 22·8; H, 2·6. $C_5H_6O_2ClI$ requires C, 23·0; H, 2·3%).

3-Chloroallyl Carbanilate.—A mixture of phenyl *iso*cyanate (1 g.) and 3-chloroallyl alcohol (2 g., prepared as described by van Romburgh, *loc. cit.*) was heated for 5 minutes at 100° and then shaken with water. When the product, which solidified on standing overnight, was collected, washed with water, dried, and crystallised from light petroleum, *3-chloroallyl carbanilate* was obtained in colourless needles, m. p. 53—54·5° (Found: C, 56·7; H, 4·6. $C_{10}H_{10}O_2NCl$ requires C, 56·7; H, 4·7%).

3-Chloroallyl Chloroformate.—After 3-chloroallyl alcohol (21·7 g.) had been added dropwise to carbonyl chloride (27 c.c.), cooled in a mixture of ice and salt, at such a rate that the temperature did not rise above 0°, the whole was left at room temperature overnight. The excess of carbonyl chloride was removed in a current of dry air at 20°, the residue was dried ($MgSO_4$), and distilled, and a liquid obtained over the range 90—160°. When this was fractionated through a short column, *3-chloroallyl chloroformate* (17·5 g.) was collected at 150—160° (Found: Cl, 45·9. $C_4H_4O_2Cl_2$ requires Cl, 45·8%). After equimolecular proportions of the product and aniline had been mixed in ether, an aqueous solution containing slightly more than a molecular proportion of potassium hydroxide was gradually added with mechanical stirring at 0°. When the ethereal solution was dried and evaporated, and the residue crystallised from light petroleum, 3-chloroallyl carbanilate separated in colourless needles, m. p. 51—52°, identical (mixed m. p.) with the above substance.

3-Chloroallyl 2-Chloroethylcarbamate.—3-Chloroallyl chloroformate (10 g.) and a solution of potassium hydroxide (7·2 g.) in water (50 c.c.) were added concurrently during about ¼ hour to a solution of 2-chloroethylamine hydrochloride (15 g.) in water (20 c.c.) which was cooled in ice-water and stirred. When the product was extracted with ether, dried, and fractionated, *3-chloroallyl 2-chloroethylcarbamate* was obtained as a colourless oil (6 g.), b. p. 156°/16 mm. (Found: C, 36·8; H, 4·7. $C_6H_9O_2NCl_2$ requires C, 36·4; H, 4·5%).

Di-(3-chloroallyloxy)methane.—After a mixture of 3-chloroallyl alcohol (18 g.), paraformaldehyde (3 g.), and anhydrous ferric chloride (0·5 g.) had been heated at 100° for 6 hours in a flask fitted with a reflux condenser, the lower aqueous layer was removed and the oily product washed twice with water (5 c.c.) before being dried (K_2CO_3). On distillation, *di-(3-chloroallyloxy)methane* was obtained as a colourless oil (7·1 g.), b. p. 108—123°/20 mm. (Found: C, 42·9; H, 5·3. $C_7H_{10}O_2Cl_2$ requires C, 42·6; H, 5·1%).

1 : 1-Di-(3-chloroallyloxy)ethane.—After powdered, anhydrous calcium chloride (3 g.) had been shaken for a few minutes with 3-chloroallyl alcohol (20 g.), the mixture was cooled to 0° and treated with acetaldehyde (5·5 g.). The whole was vigorously shaken for ½ hour at room temperature, and then left for 30 hours with occasional shaking. Water (4 c.c.) was added to dissolve the calcium chloride, and the upper oily layer was washed with water, and dried. When distilled, it gave *1 : 1-di-(3-chloroallyloxy)ethane* as a colourless oil (9 g.), b. p. 115—120°/16 mm. (Found: C, 45·1; H, 5·7. $C_8H_{12}O_2Cl_2$ requires C, 45·5; H, 5·7%).

1 : 1-Di-(3-chloroallylthio)ethane.—When a mixture of the thiol (15 g.), from 3-chloroallyl chloride, and acetaldehyde (3 g.) was cooled in ice-water and shaken for a few minutes with anhydrous zinc chloride (3 g.), an aqueous layer soon began to separate. After the whole had been left for a day, water (10 c.c.) was added, and the oily product extracted with ether. When the extract was washed with water, dried, and fractionated, *1 : 1-di-(3-chloroallylthio)ethane* was obtained as a pale yellow oil (8·5 g.), b. p. 162—164°/13 mm. (Found: C, 38·6; H, 4·7. $C_8H_{12}Cl_2S_2$ requires C, 39·5; H, 4·9%).

3-Chloroallyl Thiocyanate.—Potassium thiocyanate (9·7 g.) in water (5 c.c.) was mixed with 3-chloroallyl chloride (15·7 g.) in alcohol (50 c.c.), the solution left overnight, and then refluxed for an hour. After distillation in steam, the product was extracted with ether, dried, and fractionated. *3-Chloroallyl thiocyanate* was obtained as a colourless oil, b. p. 72—78°/0·2 mm. (Found: C, 35·2; H, 3·0. C_4H_4NClS requires C, 36·0; H, 3·0%).

3-Chloroallyl Acetyldithiocarbamate.—After a mixture of the above thiocyanate (3·3 g.), ethanethioic acid (1·9 g.), and benzene (25 c.c.) had been refluxed for 3½ hours, the solvent was removed under reduced pressure, and the residue crystallised from *sec.*-butyl alcohol. *3-Chloroallyl acetyldithiocarbamate* (4 g.)

was obtained in pale yellow plates, m. p. 105° (Found : C, 34·4; H, 3·9; S, 30·9. $C_9H_9ONClS_2$ requires C, 34·4; H, 3·8; S, 30·6%).

3-Chloroallyldichloroarsine.—3-Chloroallyl chloride (27·75 g.) was added to arsenious oxide (20 g.) dissolved in a solution of sodium hydroxide (24 g.) in water (200 c.c.), and contained in a flask fitted with a reflux condenser and mechanical stirrer (mercury seal). The mixture was gradually heated, with stirring, to 100°, at which it was kept for 3 hours. After all volatile material had been removed in steam, the residual aqueous solution was cooled, treated with concentrated hydrochloric acid (255 c.c.), and quickly filtered. A few crystals of potassium iodide were added, and sulphur dioxide passed through the solution for 3 hours. When the oily product was extracted with carbon tetrachloride, and the extract dried ($MgSO_4$) and fractionated, *3-chloroallyldichloroarsine* was obtained as an almost colourless oil (11·6 g.), b. p. 104—105°/18 mm. (Found : C, 15·6; H, 2·2; Cl, 47·7. $C_3H_4Cl_3As$ requires C, 16·2; H, 1·8; Cl, 48·1%).

We are indebted to Sir Robert Robinson for his interest in these investigations, and to the Chief Scientist, Ministry of Supply, for permission to publish the work.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, February 20th*, 1948.]

---

442. *The Preparation and Reactions of Carbonyl and Sulphuryl Fluorides and Chlorofluorides.*

By H. J. EMELÉUS and J. F. WOOD.

The preparation of carbonyl fluoride and chlorofluoride by the autoclave reaction of carbonyl chloride with antimony trifluoride is described. Sulphuryl fluoride and chlorofluoride may be similarly prepared from antimony trifluoride and sulphuryl chloride, but sulphuryl fluoride is more conveniently obtained from sulphur dioxide and argentic fluoride. Reactions of these substances are described, and it is shown that sulphuryl fluoride and chlorofluoride give no fluorinating reaction analogous to the chlorinating reaction of sulphuryl chloride catalysed by benzoyl peroxide.

CARBONYL fluoride was first prepared in a pure state by Ruff and Miltschitzky (*Z. anorg. Chem.*, 1934, **221**, 154) by the interaction of carbon monoxide and argentic fluoride. An alternative method of preparation by the reaction of carbonyl chloride with hydrogen fluoride under pressure, using antimony pentachloride as a catalyst, yields both the fluoride and the chlorofluoride, but the former is always contaminated by hydrogen chloride (Simons, Herman, and Pearlson, *J. Amer. Chem. Soc.*, 1946, **68**, 1672). Carbonyl fluoride and hydrogen chloride, b. p. −83° and −83·7° respectively, cannot be separated by distillation. The preparative method described below is based on the autoclave reaction between carbonyl chloride and antimony trifluoride. It may be made to yield either carbonyl fluoride or the chlorofluoride as the main product, and has the advantage that the preparation of carbonyl fluoride free from hydrogen chloride is possible. The carbonyl fluoride is contaminated with 5—10% of carbon dioxide, which does not interfere with the study of the reactions with certain organic compounds.

Carbonyl fluoride is hydrolysed by water to carbon dioxide and hydrogen fluoride. It attacks glass but may be handled in silica or metal apparatus. No reactions with organic compounds have been described in the literature. It is now shown that the products with aniline, methylaniline, diethylamine, ethanol, and phenol are phenylcarbamyl fluoride, *phenylmethylcarbamyl fluoride*, *diethylcarbamyl fluoride*, ethyl fluoroformate, and *phenyl fluoroformate* respectively. Buckley, Piggott, and Welch (*J.*, 1945, 864) first prepared phenylcarbamyl fluoride by the addition of hydrogen fluoride to phenyl *iso*cyanate, and Ray (*Nature*, 1933, **132**, 173) prepared ethyl fluoroformate from ethyl chloroformate and thallous fluoride : the other compounds mentioned are new. The table below compares the boiling and melting points of the analogous fluoro- and chloro-derivatives. The fluoro-compounds are in general more stable to heat and less readily hydrolysed.

Deriv. from :	Fluoro-compound.	Chloro-compound.
NH_2Ph	M. p. 32°	M. p. 58°
NHMePh	B. p. 109/14 mm.	M. p. 88 [1]
$NHEt_2$	B. p. 154	B. p. 187—190 [2]
EtOH	B. p. 57	B. p. 94
PhOH	B. p. 153	B. p. 187 (decomp.) [3]

[1] Michler and Zimmermann, *Ber.*, 1879, **12**, 1165.
[2] Lumière and Perrin, *Bull. Soc. chim.*, 1904, **31**, 689.
[3] Hentschel, *J. pr. Chem.*, 1887, **36**, 305.

In its reactions with amines and ethanol, carbonyl chlorofluoride behaved as the acid

chloride of the hypothetical fluoroformic acid. With diethylamine, methylaniline, and ethanol under suitable conditions only the carbamyl fluorides and fluoroformate were produced.

Sulphuryl fluoride was first prepared by Moissan and Lebeau (*Compt. rend.*, 1901, **132**, 374) by the direct union of fluorine and sulphur dioxide on a hot platinum wire. Traube, Hoerenz, and Wunderlich (*Ber.*, 1919, **52**, 1272) prepared it by heating barium fluorosulphonate. It has been found, however, that the compound is more conveniently prepared by the reaction of sulphur dioxide with argentic fluoride. Some investigations were also made on the autoclave reaction between sulphuryl chloride and antimony trifluoride. With antimony pentachloride as a catalyst a 25% yield of sulphuryl fluoride was obtained, the other volatile product being sulphur dioxide, which is believed to be formed by reaction of sulphuryl chloride (*a*) with the walls of the autoclave or (*b*) with the antimony trifluoride, giving quinquevalent antimony halide. In an attempt to eliminate the second of these side reactions, antimony trifluoride was replaced by antimony trifluorochloride but the formation of sulphuryl fluoride was almost completely suppressed, sulphuryl chlorofluoride being obtained in fair yield (65%). The treatment of sulphuryl chlorofluoride with fresh antimony trifluorodichloride also gave only a low yield (5%) of the fluoride, together with much sulphur dioxide. Almost half of the chlorofluoride was recovered unchanged. Most of the sulphuryl fluoride used in this investigation was made from sulphur dioxide and argentic fluoride.

Sulphuryl chlorofluoride was first prepared in an impure state by Davies and Dick (*J.*, 1932, 2042) by chlorination of toluene-*o*-sulphonyl fluoride. This reaction has now been re-examined, and the product characterised. Booth and Herrmann (*J. Amer. Chem. Soc.*, 1936, **58**, 63) described the autoclave reaction between sulphuryl chloride and antimony trifluoride, with antimony pentachloride as a catalyst. The reaction was studied in an autoclave fitted with a water-cooled head, through which the volatile products were continuously taken off. At 300°/6·5 atm. no sulphuryl fluoride was obtained, the chlorofluoride being contaminated with sulphur dioxide. Gowland (B.P. 527,713) has shown that yields of the chlorofluoride up to 90% are obtained in this reaction if a little water is used as a catalyst, but no sulphuryl fluoride results. In repeating these experiments on the preparation of sulphuryl fluoride, a closed autoclave which was not fitted with a reflux head was employed. Much higher pressures (up to 100 atm.) were observed, which may well account for the production of the fluoride (see above) as well as the chlorofluoride in the present experiments.

The chief interest in studying the reaction of sulphuryl fluoride and chlorofluoride was in their possible use as halogenating agents. Kharasch and Brown (*J. Amer. Chem. Soc.*, 1939, **61**, 2142; *Ind. Eng. Chem.*, 1944, **36**, 785) have shown that sulphuryl chloride, catalysed by benzoyl peroxide, is able to chlorinate hydrocarbons at reasonably low temperatures. Typical reactions of this type are described below in which sulphuryl fluoride has been used in place of sulphuryl chloride, but it was found that no fluorination resulted. On the other hand, the reactions of sulphuryl fluoride and chlorofluoride with diethylamine were vigorous, leading to the formation of diethylsulphamyl fluoride with sulphuryl fluoride, and diethylsulphamyl chloride with sulphuryl chlorofluoride. The former has been prepared by the fluorination of diethylsulphamyl chloride with a concentrated aqueous solution of potassium fluoride (B.P. 457,119), and the latter by the reaction between diethylamine and sulphuryl chloride (Binkley and Degering, *J. Amer. Chem. Soc.*, 1939, **61**, 3250). This difference in the behaviour of sulphuryl chloride and fluoride may be attributed to the difference in the strength of the S–Cl and S–F bonds. The catalytic reaction of benzoyl peroxide in the case of sulphuryl chloride is attributed by Kharasch to the primary formation of a phenyl radical which reacts as follows:

$$C_6H_5^{\bullet} + SO_2Cl_2 \longrightarrow SO_2Cl^{\bullet} + C_6H_5Cl$$
$$SO_2Cl^{\bullet} \longrightarrow SO_2 + Cl^{\bullet}$$
$$Cl^{\bullet} + RH \longrightarrow R^{\bullet} + HCl$$

It appears from the experiments described here that sulphuryl fluoride is sufficiently stable to resist the first step in such a reaction.

Experimental.

Fluorinations under pressure were carried out in a rotating mild steel autoclave (1500 c.c. capacity) fitted with a thermometer pocket, fine-adjustment outlet valve, and Bourdon gauge. It was gas-heated. In charging it with substances boiling below room temperature the liquefied gas was sucked into the autoclave while the latter was cooled in an ice–salt mixture. Alternatively, the autoclave was cooled by allowing liquid air to evaporate in it, and the liquified gas was poured in. The copper autoclave used in the preparation of carbonyl chlorofluoride was of the type described by Booth and Herrmann (*loc. cit.*).

The low-temperature still (Fig. 1) had a vacuum-jacketed glass tube *A* (400 mm. × 15 mm.) packed with single-turn Fenske spirals, and was surrounded by an aluminium tube to act as thermal insulator.

The still-pot, *B*, was heated in an alcohol-bath on an electric hot-plate, and the rising vapours were condensed in the still head *C* which, for gases boiling above about − 70°, was filled with a solid carbon dioxide–alcohol mixture. For temperatures below − 70° the still head was filled with a suitable liquid maintained at its m. p. by the occasional addition of liquid nitrogen. The condensed liquid passed over the tip of the thermocouple (*D*) placed against the edge of the weir at *E*. The b. p. of liquids boiling below room temperature was indicated by the minimum temperature of the refluxing liquid. A little of the refluxing liquid was retained in the tube *F* leading to the tap *G*, lubricated with a silicone grease, which was opened momentarily when the column reached equilibrium to allow some of the reflux to flow into the cooled receiver *H*. Successive quantities of distillate were drawn off in this way as equilibrium was re-established in the column.

An apparatus for the measurement of boiling points below room temperature is shown in Fig. 2. The condenser *A* was suitably cooled below the b. p. of the compound, and the liquid in *B* (2—3 c.c.) was allowed to boil gently, some of the reflux being trapped in the well *C*, whilst the bulk returned to *B* by the spill-over hole. The temperature was recorded by the thermocouple with its tip immersed in the liquid in *C*.

Preparation of Carbonyl Chlorofluoride.—Commercial antimony trifluoride (1 mol.), dried at 120° and ground to a fine powder, carbonyl chloride (4 mols. ≡ 33% excess), and antimony pentachloride (10 c.c.) were heated to 135° in the copper autoclave for one hour. The reflux head was cooled by running water at 15°. The pressure rose from an initial value of 40 lb./in.² to approx. 475 lb./in.². The gases were led off from the cold autoclave, and the carbonyl chlorofluoride and unreacted carbonyl chloride condensed in glass traps cooled in solid carbon dioxide. A small quantity of carbonyl fluoride (b. p. −83°) escaped. The condensed gases were separated by distillation in the low-temperature liquid take-off still. Carbonyl chlorofluoride (2·1 mols.) was collected at approximately −45°. The unreacted carbonyl chloride amounted to 1·4 mols. The calculated yield of carbonyl fluoride was 0·3 mol. The carbonyl chlorofluoride was stored in glass globes attached to a vacuum system. It was re-fractionated three times, and the head and tail thirds rejected each time. The final middle fraction was taken back into the vacuum system and used for analysis and the measurement of vapour pressures and of the molecular weight by the Regnault method. After the molecular-weight determination, the weighed sample of gas was quantitatively transferred in the vacuum system to a vessel containing an excess of alcoholic potassium hydroxide. The chloride in the resulting solution of potassium carbonate, fluoride, and chloride was determined by titration using Pugh's method (*J.*, 1937, 1824), which is valid for the determination of chlorides in the presence of fluorides (Found: Cl, 43·0; *M*, 83·6, 83·2. Calc. for COClF: Cl, 43·0%; *M*, 82·5). The vapour-pressure measurements over the range −46·3° to −116·5° were made by the static method, using a silica U-tube manometer and a vapour-pressure finger. The carbonyl chlorofluoride was thus only in contact with silica and mercury throughout the series of measurements. The mercury pressure was measured with a cathetometer, and the temperatures with suitable vapour-pressure thermometers (ethylene, carbon dioxide, and ammonia).

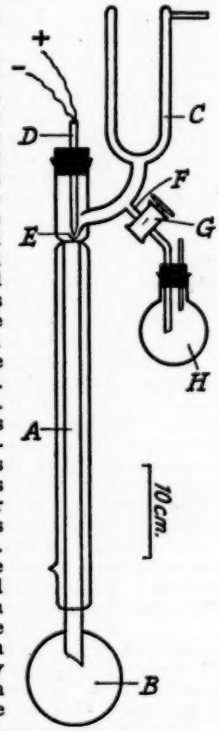


FIG. 1.

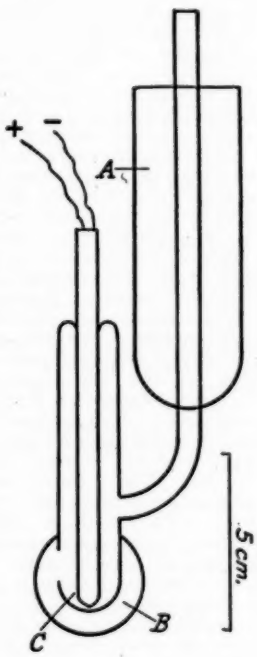


FIG. 2.

The data are represented by the equation $\log P$ (mm.) $= 7{\cdot}9235 - 1151{\cdot}5/T$, where T is in °K., the calculated b. p. being −45·0° ± 0·2°.

Preparation of Carbonyl Fluoride.—Carbonyl chloride (3 mols.) and antimony trifluoride (3·75 mols. ≡ 50% excess) were heated in the rotating autoclave for 12 hours. In certain runs, and in certain preparations of carbonyl chlorofluoride, bromine or antimony pentachloride was added to test its effect as a catalyst, but these appeared to have little influence on the ease of reaction. In the particular run described, antimony pentachloride was not added. The autoclave was kept between 200° and 280°, and the pressure rose to 150 atm. The pressure in the cold autoclave was 40 atm. The gas was freed from carbonyl chloride and chlorofluoride by passage through copper traps cooled in solid carbon dioxide. The purity of the carbonyl fluoride was determined as follows: The gas was slowly passed down a silver tube into a tared flask containing a known excess of standard alkali, the quantity of gas absorbed being found by the increase in weight of the solution; the solution was back titrated by standard hydrochloric acid in the cold to the phenolphthalein end-point, and was then heated to its boiling point to decompose the bicarbonate, and the titration continued until the pink colour of the phenolphthalein failed to reappear on further boiling. The first titration value depended on the quantity of carbon dioxide in the carbonyl fluoride, and the second value on the fluoride content of the solution, *i.e.*, on the carbonyl fluoride. As a check, one solution was analysed for fluorine by quantitative precipitation as calcium fluoride. Values obtained in various runs were COF_2 = 89·5, 92·5, 90·5; 95·2 (as CaF_2); CO_2 = 6·5, 5·5, 8·5%. The figures for carbon dioxide are uncertain owing to uncertainties in the first end-point and the percentages

do not total 100%. However, it is apparent that carbonyl fluoride prepared by this method is 90—95% pure. The hydrolysed solution did not contain chloride and hence the carbonyl fluoride was free from hydrogen chloride.

Reactions of Carbonyl Fluoride.—(1) *With aniline: preparation of phenylcarbamyl fluoride.* Carbonyl fluoride, from the autoclave, was purified by passage through two copper traps cooled in solid carbon dioxide. The gas was bubbled through ether (100 c.c.) into which was slowly dropped a solution of aniline (5 g.) in ether (50 c.c.). Considerable quantities of diphenylurea were formed and tended to clog the tip of the dropping funnel. When all the aniline had been added, the urea and aniline hydrofluoride were filtered off and the ether evaporated off in a vacuum. The solid residue of phenylcarbamyl fluoride was crystallised from ether–pentane (Found: N, 10·0. Calc. for C_7H_6ONF: N, 10·1%). The solid gave no depression of m. p. (32°) when mixed with a sample of phenylcarbamyl fluoride prepared by the addition of hydrogen fluoride to phenyl *iso*cyanate. On hydrolysis with water, a solution of hydrofluoric acid was obtained together with a white crystalline solid, diphenylurea (m. p. 238°).

(2) *With methylaniline: preparation of phenylmethylcarbamyl fluoride.* An excess of carbonyl fluoride was passed into a solution of methylaniline (5 g.) in benzene (50 c.c.). The liberated hydrogen fluoride was absorbed on sodium fluoride. The solids formed were filtered off, the benzene evaporated, and the liquid residue distilled in a vacuum (b. p. 103—109°/14 mm.). On redistillation, the main fraction (b. p. 109°/14 mm.) was analysed (Found: C, 62·8; H, 5·2; N, 9·0. C_8H_8ONF requires C, 62·9; H, 5·2; N, 9·2%). *Phenylmethylcarbamyl fluoride* is a colourless liquid when pure, but on exposure to moist air it turns green then purple. It is stable to glass and is hydrolysed only on prolonged boiling with water to hydrofluoric acid and *NN'*-diphenyl-*NN'*-dimethylurea. It has a peculiar odour, and exposure to the vapours causes temporary contraction of the pupils of the eyes.

(3) *With diethylamine: preparation of diethylcarbamyl fluoride.* A similar reaction between carbonyl fluoride and diethylamine gave *diethylcarbamyl fluoride* (b. p. 154°) (Found: C, 51·1; H, 8·9; N, 11·3. $C_5H_{10}ONF$ requires C, 50·4; H, 8·4; N, 11·8%). The compound is slowly decomposed by water to give hydrogen fluoride and tetraethylurea.

(4) *With ethanol: preparation of ethyl fluoroformate.* Carbonyl fluoride was bubbled through a mixture of ethanol (5 g.), toluene (30 c.c.), and pyridine (10 g.). The white pyridine compounds were filtered off, and the ethyl fluoroformate distilled out of the solution (b. p. 57°). The molecular weight was determined by Regnault's method (Found: *M*, 91·6. Calc. for $C_3H_5O_2F$: *M*, 92). By reaction with an aqueous solution of sodium *p*-hydroxybenzoate, the white crystalline compound *p*-carboxyphenyl ethyl carbonate was obtained. There was no depression of m. p. when the compound was mixed with the product of a similar reaction between ethyl chloroformate and sodium *p*-hydroxybenzoate (Found: C, 56·8; H, 4·7. Calc. for $C_{10}H_{10}O_5$: C, 57·1; H, 4·76%).

(5) *With phenol: preparation of phenyl fluoroformate.* No reaction occurred when carbonyl fluoride was passed into a solution of phenol in ether. A similar reaction with phenol (3 g.) in benzene (50 c.c.) and pyridine (10 c.c.) gave a quantitative yield of diphenyl carbonate. Carbonyl fluoride (10 c.c. of liquid at −95°), phenol (10 g.), and benzene (25 c.c.) were heated in a small tube autoclave for one hour at 100°. The solution was filtered through sodium fluoride to remove hydrogen fluoride, and the benzene evaporated off. The *phenyl fluoroformate* distilled off between 145° and 155°. On redistillation, 7·5 g. of liquid (b. p. 153°) were obtained (Found: C, 60·2; H, 4·0. $C_7H_5O_2F$ requires C, 60·0; H, 3·6%). Phenyl fluoroformate is a colourless lachrymatory liquid. It slowly attacks glass, presumably because of traces of water, by which it is hydrolysed to diphenyl carbonate and hydrogen fluoride. It is quite stable at the b. p., unlike phenyl chloroformate which decomposes into diphenyl carbonate and carbonyl chloride.

Reactions of Carbonyl Chlorofluoride.—(1) *With ethanol.* Ethanol (3 g.) was dropped on liquid carbonyl chlorofluoride (10 g.) cooled in solid carbon dioxide. The excess of gaseous reagent was evaporated off, and the residue fractionated. Considerable etching of the flask occurred, but two distinct fractions were obtained. They were ethyl fluoroformate (3 g.), boiling in the range 52—58°, and diethyl carbonate (1·5 g.) (b. p. 125°). No ethyl chloroformate (b. p. 94°) was obtained.

(2) *With methylaniline.* A solution of methylaniline (8 g.) in ether (75 c.c.) was added dropwise to a solution of carbonyl chlorofluoride (10 g.) in ether (25 c.c.) cooled in solid carbon dioxide. A white precipitate was formed but most of this redissolved when the excess gas was boiled off. The ether was evaporated, and the liquid phenylmethylcarbamyl fluoride distilled off in a vacuum (b. p. 110°/15 mm.). A small quantity of tarry material remained in the flask. 10 G. of phenylmethylcarbamyl fluoride were obtained, representing a yield of 88% on the reaction $NHMePh + COClF = NMePh{\cdot}COF + HCl$.

(3) *With diethylamine.* An ethereal solution of diethylamine (30 g.) was similarly caused to react with carbonyl chlorofluoride (11 g.). The reaction was extremely vigorous even at −78°. The white precipitate of diethylamine hydrochloride was filtered off, and the diethylcarbamyl fluoride separated by distillation. The latter was obtained in 45% yield based on the reaction $2NHEt_2 + COClF = NEt_2{\cdot}COF + NHEt_2{,}HCl$.

The Preparation of Sulphuryl Chlorofluoride.—(a) *Chlorination of toluene-o-sulphonyl fluoride.* Toluene-*o*-sulphonyl fluoride (50 g.), prepared as described by Davies and Dick (*loc. cit.*), was chlorinated at a temperature between 145° and 160° for an aggregate time of 45 hours. The exit gases (approx. 250 g.) were collected in glass traps cooled in solid carbon dioxide. The bulk of this was chlorine, but on fractionation in the low-temperature still a small quantity (1 g.) of sulphuryl chlorofluoride was obtained. It was freed from chlorine by repeated distillation and condensation from traps cooled to −20°, and analysed for chlorine as described by Booth and Herrmann (*loc. cit.*) (Found: Cl, 30·1, 30·0. Calc. for SO_2ClF: Cl, 29·9%). The molecular weight was determined by Regnault's method and the b. p. measured in the separate apparatus already described (Found: *M*, 119·0; b. p. + 7·6°. SO_2ClF has *M*, 118·5, b. p. + 7·6°). The liquid and solid products from the chlorination were not examined further.

(b) *Fluorination of sulphuryl chloride.* (i) Sulphuryl chloride (7·4 mols.) and antimony trifluoride (2·9 mols.) together with antimony pentachloride (50 g.) as catalyst were heated in the rotating autoclave for 3 hours at 220—260°. The pressure rose to 100 atm. The gases were led off from the cold autoclave

and collected in glass traps cooled in solid carbon dioxide. The mixture of sulphuryl fluoride (b. p. −55°), sulphur dioxide (b. p. −10°), and sulphuryl chlorofluoride (b. p. 7·6°) was separated by fractionation in the low-temperature still. Yields were: SO_2F_2 0·1 mol., SO_2 3·8 mols., SO_2ClF 3·4 mols. (46%).

(ii) A mixture of chlorine (2·9 mols.) and antimony trifluoride (2·9 mols.) was heated in the rotating autoclave to form SbF_3Cl_2. The autoclave was evacuated, and the sulphuryl chloride (7·4 mols.) syphoned on to the fluorinating agent. The mixture was heated as before, and the products separated. Yields were: SO_2F_2 0·15 mol., SO_2 1·8 mols., SO_2ClF 5·3 mols. (72%). A combined sample from these two preparations was analysed as before (Found: Cl, 29·5, 29·8. Calc. for SO_2ClF: Cl, 29·9%).

Preparation of Sulphuryl Fluoride.—(a) *Fluorination of sulphur dioxide.* Fluorine was passed over coarsely powdered silver fluoride (180 g.) in a copper tube heated to about 180°. The current in the fluorine generator was 25 amps. After 4 hours, when no further gas appeared to be absorbed, the argentic fluoride was cooled to room temperature in a slow stream of fluorine. Sulphur dioxide was passed over the argentic fluoride and a mixture of excess sulphur dioxide and sulphuryl fluoride was collected in glass traps cooled in solid carbon dioxide. The reaction was strongly exothermic and the sulphur dioxide was passed until the copper tube and contents regained room temperature. The sulphuryl fluoride was separated by fractionation in the low-temperature still. The fraction boiling between −56° and −53° was refractionated. The bulk (33 g.) boiled at −55°. The identity of the compound was confirmed by analysis. A pure sample was weighed in the Regnault bulb and quantitatively transferred to a vessel containing an excess of alcoholic potassium hydroxide. The gas was hydrolysed to potassium fluoride and fluorosulphonate. The solution was transferred to a platinum dish and evaporated to dryness on a steam-bath to hydrolyse the fluorosulphonate to fluoride and sulphate. An excess of concentrated hydrochloric acid was added, and the solution again evaporated to dryness to remove the fluoride as hydrogen fluoride. The resulting solution, free from fluoride, was analysed for sulphate by precipitation with barium chloride in the usual way (Found: S, 31·3; *M*, 101. Calc. for SO_2F_2: S, 31·4%; *M*, 102).

(b) *Fluorination of sulphuryl chloride.* (i) Sulphuryl chloride (4 mols.), antimony pentachloride (50 g.), and an excess of antimony trifluoride (3·5 mols.) sufficient to replace both halogen atoms were heated in the rotating autoclave for 7 hours at about 260°. The pressure rose to 100 atm. The gaseous products were fractioned in the usual way and found to consist of sulphuryl fluoride (1·0 mol. ≡ 25%) and a large quantity of sulphur dioxide (2·3 mols. ≡ 57%). No sulphuryl chlorofluoride was obtained.

(ii) Sulphuryl chloride (7·4 mols) and antimony trifluorodichloride (3·5 mols) were heated as before in the rotating autoclave. The gases were fractionated in the usual way. The yields obtained were: sulphur dioxide (1·4 mols.), sulphuryl fluoride (5 g.), and sulphuryl chlorofluoride (4·8 mols. ≡ 65%).

(c) *Fluorination of sulphuryl chlorofluoride.* (i) Sulphuryl chlorofluoride (2·1 mols.), antimony trifluoride (2·1 mols.), and antimony pentachloride (25 g.) were heated in the rotating autoclave for 5 hours at 250°. On fractionation of the products, unchanged sulphuryl chlorofluoride (0·90 mol.), sulphur dioxide (0·94 mol.), and sulphuryl fluoride (0·16 mol. ≡ 8%) were obtained.

(ii) Sulphuryl chlorofluoride (2 mols.) and antimony trifluorodichloride (1 mol.) were heated as above in the rotating autoclave. A mixture of unchanged sulphuryl chlorofluoride (0·85 mol.), sulphur dioxide (0·34 mol.), and sulphuryl fluoride (0·10 mol. ≡ 5%) was obtained.

Reactions of Sulphuryl Chlorofluoride and Fluoride.—(1) *With hydrocarbons.* No reaction occurred when sulphuryl fluoride was bubbled through boiling hexane or toluene containing 1% of benzoyl peroxide, or when sulphuryl fluoride and chlorofluoride were heated with hexane (containing 1% of benzoyl peroxide) under pressure at 130—150°. When sulphuryl chlorofluoride (90 g.), benzene (65 g.), and aluminium chloride (1 g.) were heated under pressure at 130° most of the benzene (63 g.) was recovered unchanged. A small quantity of chlorobenzene (Found: Cl, 31·3. Calc. for C_6H_5Cl: Cl, 31·5%) was obtained but there was no trace of fluorobenzene.

(2) *With 1:2-dichloroethylene.* No reaction occurred when sulphuryl chlorofluoride was heated under pressure with dichloroethylene containing 1% of benzoyl peroxide.

(3) *With phenol.* No fluorination took place when sulphuryl fluoride was bubbled through a boiling solution of phenol (10 g.) in chloroform (50 ml.) containing a little iodine (1 g.). Similarly no halogenation occurred when sulphuryl chlorofluoride (20 ml.) was heated under pressure with a solution of phenol (10 g.) and benzoyl peroxide (1 g.) in chloroform (15 ml.).

(4) *With diethylamine.* (a) A solution of diethylamine (40 ml.) in ether (50 ml.) was dropped into a solution of sulphuryl fluoride (23 g.) in ether (50 ml.) cooled in dry ice. A vigorous reaction took place with formation of a white precipitate of diethylamine hydrofluoride. The mixture was warmed to room temperature, and the solid filtered off. The ether was evaporated from the filtrate, and the residue distilled in a vacuum (b. p. 72°/14 mm.). A colourless liquid was obtained which was stable to water but gave a solution containing fluoride on prolonged boiling with concentrated sodium hydroxide solution. The elements nitrogen and sulphur were shown to be present by fusion with sodium followed by the usual tests. Analysis by standard microanalytical methods showed that the liquid was diethylsulphamyl fluoride (Found: C, 31·2; H, 6·5; N, 8·8. Calc. for $C_4H_{10}O_2NSF$: C, 30·9; H, 6·45; N, 9·0%). The compound was obtained in an overall yield of 35% based on the diethylamine.

(b) A solution of diethylamine (35 g.) in ether (25 ml.) was similarly treated with sulphuryl chlorofluoride (25 ml.) in ether (25 ml.). The white precipitate (approx. 25 g.) obtained was diethylamine hydrochloride. The ether was evaporated, and the liquid residue distilled in a vacuum. The distillate (15 g.) boiled over the range 70—110°/18 mm. A quantity of black tar remained in the distillation flask. On redistillation, a few drops of liquid (b. p. 70—85°/15 mm) were obtained and were shown by sodium fusion to contain nitrogen, sulphur, and fluorine, but the quantity was insufficient to permit positive identification as diethylsulphamyl fluoride (b. p. 72°/14 mm.). The major fraction boiling in the range 90—100°/15 mm. was refractionated, and the portion, b. p. 97°/13 mm., shown to be free from fluoride. This colourless liquid was readily hydrolysed by water to give a solution containing chloride. It also contained nitrogen and sulphur and analysis confirmed it as diethylsulphamyl chloride (Found: C, 28·0; H, 5·85; N, 7·9; Cl, 21·2. Calc. for $C_4H_{10}O_2NSCl$: C, 28·0; H, 5·8; N, 8·1; Cl, 20·7%).

The work on the reaction of hexane and toluene with sulphuryl fluoride was carried out in collaboration with Dr. B. C. Saunders and Mr. F. L. M. Pattison. One of the authors (J. F. W.) wishes to thank I.C.I. Ltd. (Dyestuffs Division) for a Maintenance Grant.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, January 22nd*, 1948.]

---

443. *The Reaction of Bromine Trifluoride and Iodine Pentafluoride with Carbon Tetrachloride, Tetrabromide, and Tetraiodide and with Tetraiodoethylene.*

By A. A. BANKS, H. J. EMELÉUS, R. N. HASZELDINE, and V. KERRIGAN.

Liquid bromine trifluoride reacts with carbon tetrachloride or tetrabromide forming mixtures of chlorofluoromethanes or bromofluoromethanes, the proportions of which depend on the reaction conditions. With carbon tetraiodide, bromofluoromethanes and carbon tetrafluoride result. Iodine pentafluoride converts carbon tetrabromide into a mixture of bromofluoromethanes, while with carbon tetraiodide *iodotrifluoromethane* (CIF_3) (b. p. −22·5°) is formed in good yield. Tetraiodoethylene and iodine pentafluoride give *iodopentafluoroethane* (C_2IF_5) (b. p. 13°). Preliminary experiments show these two monoiodo-compounds to differ greatly from methyl and ethyl iodides in their reactivity, notably in their inability to form Grignard compounds under the usual conditions. By reaction of the iodo-compounds with mercury the compounds *trifluoromethylmercuric iodide*, m. p. 112·5°, and *pentafluoroethylmercuric iodide*, m. p. 87·5—88·5°, have been prepared.

THIS investigation had as its object the comparison of the reactivities of bromine trifluoride and iodine pentafluoride by a study of their reactions with fully halogenated methanes, and the synthesis of the compounds CIF_3 and C_2IF_5, from which it was hoped to prepare organometallic derivatives. Previous work on the reactions of the halogen fluorides with halogenated methanes is scanty. Nutting and Petrie (U.S.P. 1,961,622, 1934) studied the reaction between bromine trifluoride and carbon tetrachloride, showing that chlorofluorides are formed. Their results have been confirmed and considerably extended. Ruff and Keim (*Z. anorg. Chem.*, 1931, **201**, 245) obtained trichlorofluoromethane and a small quantity of dichlorodifluoromethane by the interaction at 30—35° of iodine pentafluoride and carbon tetrachloride, while Simons, Bond, and McArthur (*J. Amer. Chem. Soc.*, 1940, **62**, 3477) isolated hexafluoroethane from the reaction products formed by heating iodine pentafluoride and carbon tetraiodide in a copper vessel. As is shown below, this reaction when carried out in glass yields *iodotrifluoromethane*, which probably reacts with copper, forming the fluorocarbon.

In the reaction between bromine trifluoride and carbon tetrachloride in a system at atmospheric pressure it is found that the volatile partly-fluorinated products, trichlorofluoromethane and dichlorodifluoromethane, are readily formed. To obtain good yields of chlorotrifluoromethane the reaction must be carried out in an autoclave. The bromofluoromethanes are less well known, the mono- and di-fluoro-derivatives (b. p.s 107° and 24·5°, respectively) having been prepared by Rathsburg (*Ber.*, 1918, **51**, 669) by refluxing carbon tetrabromide with excess of argentic fluoride. The trifluoro-derivative (b. p. −59° to −60·5°) was first prepared by Brice, Pearlson, and Simons (*J. Amer. Chem. Soc.*, 1946, **68**, 968) by the thermal bromination of the monohydrogen fluorocarbon. Reaction between bromine trifluoride and carbon tetrabromide occurred smoothly, and because of the comparatively high boiling points of the intermediates, the tri- as well as the mono- and di-fluoro-compounds could be prepared without the use of an autoclave. Bromine trifluoride and carbon tetraiodide reacted very readily but in this case no iodofluoromethanes were isolated. The fluorinating action of iodine pentafluoride proved to be much milder, the production of bromofluoromethanes from carbon tetrabromide paralleling Ruff and Keim's observations on the tetrachloride. Iodine pentafluoride proved also to be a suitable reagent for the fluorination of iodo-derivatives, and the production of iodotrifluoromethane by the interaction of this substance and carbon tetraiodide presented no difficulty. Hexaiodoethane is not known, but tetraiodoethylene and iodine pentafluoride yielded *iodopentafluoroethane*. This reaction was much more difficult to control.

In the fluorination of halogenated methanes it is remarkable that no products are formed in which there are two or more carbon atoms in the molecule. This indicates that organic free radicals play no significant rôle in the reaction mechanism, which probably consists of a stepwise substitution by fluorine; *e.g.*,

$$CCl_4 + BrF_3 \longrightarrow BrF_2 + CCl_3F$$
$$BrF_2 + CCl_3F \longrightarrow BrF + CCl_2F_2, \text{ etc.}$$

The synthesis of the compounds CIF_3 and C_2IF_5 raises many interesting possibilities in view of the great variety of reactions shown by the analogous hydrogen compounds CH_3I and C_2H_5I. A number of the reactions of the iodofluoro-compounds are being studied and will be described later. Two *mercury* derivatives, $HgCF_3I$ and HgC_2F_5I, the preparation of which is described below, serve to establish the fact that a stable bond between the CF_3 or C_2F_5 radicals and a metal such as mercury can be formed, though it has not yet proved possible to prepare a Grignard compound by the standard procedures.

Experimental.

Reaction of Bromine Trifluoride with Carbon Tetrachloride.—Bromine trifluoride, prepared from the elements and purified by distillation at atmospheric pressure in a steel retort, was distilled from a weighed copper vessel at 110° in a stream of dry nitrogen (4 l./hr.) into 154 g. (1 mol.) of dry carbon tetrachloride in a water-cooled copper trap. The total quantity added was 46 g. (0·33 mol.) and a vigorous reaction occurred as each drop fell into the carbon tetrachloride. The gaseous reaction products were carried off in the nitrogen stream and condensed in two Pyrex traps cooled to −80° and −190° respectively. The whole of the volatile product condensed at −80°, and was re-evaporated in a stream of nitrogen, passed through a scrubber containing an alkaline sodium sulphite solution to remove free halogens, and recondensed. The residue in the reaction vessel was similarly treated with alkaline sodium sulphite, giving a product which was combined with the −80° fraction and distilled from metallic calcium through a low-temperature column packed with Fenske rings. The following fractions were obtained: (*a*) 4 g., b. p. −27·6°, *M*, 121 (CCl_2F_2, b. p. −28°, *M*, 121); (*b*) 80 g., b. p. 23·5°, *M*, 137 (CCl_3F, b. p. 23·7°, *M*, 137·4); (*c*) 50 g., b. p. 76°. Fraction (*c*) was unchanged carbon tetrachloride.

This procedure was modified by freezing 18·5 g. (0·135 mol.) of bromine trifluoride in solid carbon dioxide in a copper vessel fitted with a reflux condenser at 0° and adding slowly 18·5 g. (0·225 mol.) of carbon tetrachloride. Reaction occurred on allowing the reactants to warm slowly to room temperature. The products, separated and identified as before, were: CCl_3F, 4·5 g.; CCl_2F_2, 21 g. A similar experiment, using a reflux condenser cooled to −80°, gave from 16 g. (0·12 mol.) of bromine trifluoride and 20·6 g. (0·15 mol.) of trichlorofluoromethane, 17·5 g. of dichlorodifluoromethane, equivalent to a 96% yield on the trichlorofluoromethane used.

To prepare more fully fluorinated products a 200-c.c. stainless-steel autoclave fitted with a pressure gauge and needle valve was used. The bromine trifluoride was put into the autoclave in a separate container and the reactants were not mixed until the autoclave was sealed. The yields of four experiments recorded below show that under these conditions, which preclude the escape of the volatile partly fluorinated products as formed, moderate yields of monochlorotrifluoromethane result.

Wt. of CCl_4, g.	Wt. of BrF_3, g.	Wt. of $CClF_3$, g.	Wt. of CCl_2F_2, g.	Wt. of CCl_4, g.	Wt. of BrF_3, g.	Wt. of $CClF_3$, g.	Wt. of CCl_2F_2, g.
78	78	34·4	19·4	38·5	41	21·9	4·1
40	35	16	11·5	40	33·7	21·8	5·9

Reaction of Bromine Trifluoride with Carbon Tetrabromide.—As carbon tetrabromide is a solid it was fluorinated in bromine solution, 111 g. (0·33 mol.) being dissolved in 1000 g. of bromine in a 1-l. flask fitted with a stirrer and cooled in ice. With the slow addition of 15·2 g. (0·11 mol.) of bromine trifluoride, only a trace of volatile material collected in cooled traps connected with the flask. The bulk of the bromine was distilled off through a column, and the residue was washed with alkaline sodium sulphite solution, dried, and distilled. The products were tribromofluoromethane, 85 g., b. p. 106° (Found: Br, 88·2. Calc. for CBr_3F: Br, 88·75%), and *ca.* 1 c.c. of dibromodifluoromethane (Found: *M*, 211. Calc. for CBr_2F_2: *M*, 211). The vapour-pressure data of a carefully purified sample of tribromofluoromethane in the range 43—103° are represented by the equation $\log p$ (mm.) = 7·60757 − 1796·45/*T* − 0·003284 log *T*, giving a calculated b. p. of 106·2°, a latent heat of vaporisation at the b. p. of 5·96 kcals./mol., and a value of Trouton's constant 22·1.

By varying the proportion of reactants it was possible to raise the yield of dibromodifluoromethane; *e.g.*, using 166 g. (0·5 mol.) of carbon tetrabromide in 1000 g. of bromine, reaction at 0° with 46 g. (0·33 mol.) of bromine trifluoride gave 79 g. of CBr_2F_2, 14 g. of CBr_3F, and 150 c.c. (gas) of $CBrF_3$. By dispensing with the solvent the yield of the trifluoro-compound was much increased. By adding 13·7 g. (0·1 mol.) of bromine trifluoride dropwise to 33·2 g. (0·1 mol.) of solid carbon tetrabromide, 2·1 l. (gas) of the trifluoro-compound were obtained, the yield being 94% of theoretical. A sample of this material was carefully purified by fractionation in the vacuum apparatus, and the vapour pressure was found to be represented in the range −117° to −55° by the equation $\log p$ (mm.) = 16·0750 − 1250·75/*T* − 3·1651 log *T*. The calculated b. p. is −57·8°, the latent heat of vaporisation at the b. p. 5·43 kcals./mol., and Trouton's constant 21·1.

Reaction of Bromine Trifluoride with Carbon Tetraiodide.—Carbon tetraiodide was prepared by Walker's method (*J.*, 1904, **85**, 1090) and dried in a high vacuum over phosphoric oxide for several hours. The reaction was carried out in a 250-c.c. two-necked flask with a reflux condenser, low-temperature traps, and a dropping device for adding bromine trifluoride. To 65 g. (0·125 mol.) of carbon tetraiodide cooled in ice were added dropwise during two hours 33 g. (0·24 mol.) of bromine trifluoride. A flame was seen as each drop came into contact with the tetraiodide. After the reaction the volatile products remaining in the flask were swept out in nitrogen, condensed, scrubbed with alkaline sodium sulphite solution, and stored as gas (vol., 1·8 l.). The residue in the flask contained iodine and its monobromide and pentafluoride, but no carbon tetraiodide. Two pure products, CBr_2F_2 (4·5 g.) and CF_4 (3·2 g.), were separated from the gaseous mixture formed in the reaction. There was no evidence of the formation of iodofluoromethanes.

Reaction of Iodine Pentafluoride with Carbon Tetrabromide.—Iodine pentafluoride was prepared from the elements. There was no reaction at room temperature between 52 g. (0·23 mol.) of iodine penta-

fluoride and 120 g. (0·36 mol.) of carbon tetrabromide when these were mixed in a quartz flask, the neck of which was cooled to give a reflux, and connected to cooled traps. Reaction occurred on heating gradually to 90° and after 3 hours at this temperature the volatile products remaining in the flask were swept into the traps by a stream of nitrogen. From the residue 2 g. of tribromofluoromethane (b. p. 105°) were isolated. The gaseous products (7·01 l.) gave 6·73 l. of dibromodifluoromethane (an 83% yield on the CBr_4 used) and 0·5 c.c. (liquid) of tribromofluoromethane, together with a small amount of carbon tetrafluoride.

Reaction of Iodine Pentafluoride with Carbon Tetraiodide.—To a 250-c.c. Pyrex flask containing 80 g. (0·153 mol.) of carbon tetraiodide were added 30 g. (0·135 mol.) of iodine pentafluoride. The flask was clamped in a vibrator, and connected by rubber tubing to a series of traps cooled in liquid air. Shortly after mixing the reactants a vigorous reaction with gas evolution started. This was completed, when it had moderated, by heating to 90—100° for 30 minutes. The residue in the flask consisted of iodine, iodine pentafluoride, and some unidentified material which was possibly a thermal decomposition product from carbon tetraiodide. The volatile reaction products were washed with 5% aqueous sodium hydroxide solution to remove silicon tetrafluoride, iodine, and acid vapours. The gaseous products were fractionated and gave 2·53 l. (gas) of *iodotrifluoromethane* (Found: I, 64·2; *M*, 196. CIF_3 requires I, 64·8%; *M*, 196) and 73 c.c. (gas) of trifluoromethane, which was characterised by vapour-pressure measurements. The second product may have arisen from the presence of iodoform in the carbon tetraiodide. The vapour-pressure curve of iodotrifluoromethane was measured, the data in the range −85° to −23° being represented by the equation $\log p$ (mm.) $= 7{\cdot}5665 - 1174{\cdot}29/T$. The calculated b. p. is −22·5°, the latent heat of vaporisation at the b. p. 5·357 kcals./mol., and Trouton's constant 21·4. Unsuccessful attempts were made to isolate di-iododifluoromethane and tri-iodofluoromethane by reducing the ratio of iodine pentafluoride to carbon tetraiodide and by slower addition of the pentafluoride.

Reaction of Iodine Pentafluoride with Tetraiodoethylene.—Di-iodoacetylene was prepared by Dehn's method (*J. Amer. Chem. Soc.*, 1911, **33**, 1598) and converted into tetraiodoethylene by refluxing with iodine in toluene solution (Datta and Prasad, *ibid.*, 1917, **39**, 451). To 100 g. (0·19 mol.) of tetraiodoethylene in a 500-c.c. silica flask fitted with a reflux condenser and cooled in ice, were added dropwise, during 9 hours, 180 g. (0·81 mol.) of iodine pentafluoride. Too rapid addition of the pentafluoride resulted in an explosion, the iodoethylene decomposing into carbon and iodine. A smooth reaction occurred under the correct conditions and the volatile products were condensed in the usual way in cooled traps. Towards the end of the reaction the temperature was raised gradually to 130°.

The volatile reaction products were fractionated in a vacuum apparatus and found to consist of silicon tetrafluoride and carbon dioxide (from attack on the silica vessel), tetrafluoroethylene, an unidentified fraction, and iodopentafluoroethane (12 g., 26%). The residue in the flask consisted of iodine, carbon, and unchanged iodine pentafluoride. No higher-boiling iodofluoro-compounds were present. The tetrafluoroethylene was identified by its molecular weight, vapour-pressure curve, and its reaction with chlorine to yield dichlorotetrafluoroethane (*M*, 170, b. p. 5°; cf. Henne, *J. Amer. Chem. Soc.*, 1934, **56**, 1726). *Iodopentafluoroethane* was identified by its molecular weight and iodine content (Found: I, 51·2; *M*, 246. C_2IF_5 requires I, 51·6%; *M*, 246). The b. p. of a purified sample was 13°.

Reaction of Iodotrifluoromethane with Mercury.—A known quantity of iodotrifluoromethane was condensed in vacuum into a Carius tube of 45—55 c.c. capacity containing a known weight of mercury, and the tube was sealed. A series of experiments was made with tubes of either Monax glass or silica, exposed either to daylight or to a mercury arc, or with the tube heated at a definite temperature in a rocking furnace. During irradiation the tube was clamped in a 50-cycle vibrator. After reaction the tube was cooled in liquid air, opened, and its volatile contents removed to a vacuum system for examination. The volatile residues contained unchanged iodotrifluoromethane, recovery of which varied from 70 to 94% in a series of fourteen experiments under varied conditions. This unchanged material was condensed in vacuum by passing through a trap cooled in melting pentane and was characterised by determination of molecular weight and vapour pressure. A second fraction of the volatile material passed through the pentane-bath and was condensed in liquid air. This was shown to consist of hexafluoroethane (a pure sample of which was isolated) admixed with an impurity of lower molecular weight, which may have been tetrafluoroethylene.

The residue in the Carius tube was scraped out, mercury was removed by filtration, and the remaining material was extracted with acetone. The residue consisted of finely divided mercury and mercurous iodide. The acetone solution on evaporation gave a white crystalline substance admixed with a little mercuric iodide. It was purified by sublimation and identified by analysis as *trifluoromethylmercuric iodide*, m. p. 112·5° (Found: C, 3·42; I, 31·95; F, 14·2; Hg, 50·5. CIF_3Hg requires C, 3·02; I, 32·02; F, 14·37; Hg, 50·6%). The yield of this compound varied from about 5 to 8%, a high proportion of iodotrifluoromethane being recovered unchanged. The compound is decomposed by ultra-violet light, and it is best to use a Monax tube at 1 ft. from the arc (a Hanovia fluorescence lamp fitted with an S. 250 type self-starting arc), with an irradiation time of 24—48 hours. Satisfactory yields were also obtained in the rocking-tube furnace, with up to 48 hours' heating at 180—190°.

Reaction of Mercury with Iodopentafluoroethane.—The same procedure in filling and opening the Carius tube was used as in the preparation of trifluoromethylmercuric iodide. A mixture of 4·18 g. of iodopentafluoroethane was heated for 12 hours at 205° with 65 g. of mercury in a rocking furnace. At the end of the reaction, white needle-shaped crystals separated from the excess of iodofluoride. The volatile material removed from the tube contained 94% of the iodopentafluoroethane taken. The residue in the tube was extracted with ether, and crude *pentafluoroethylmercuric iodide* recovered from the solvent. This material was sublimed and formed white plates, m. p. 87·5—88·5° (Found: C, 5·7; I, 27·5; Hg, 44·5. C_2IF_5Hg requires C, 5·4; I, 28·3; Hg, 44·9%). Irradiation of the reactants under the conditions already described for trifluoromethylmercuric iodide gave from 1·80 g. of iodopentafluoroethane and 40 g. of mercury, 0·04 g. of the resublimed mercurial, 67% of the iodofluoro-compound being recovered unchanged.

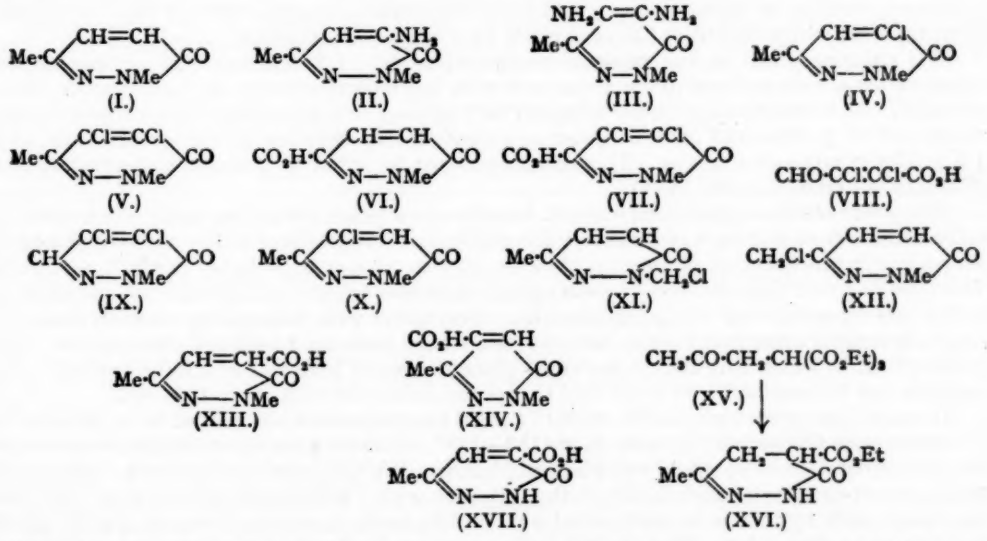
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 16th*, 1948.]

444. *The Conversion of Sucrose into Pyridazine Derivatives. Part III. Constitutional Studies on the Products of Chlorination of 2 : 6-Dimethyl-3-pyridazone.*

By R. F. Homer, Hilda Gregory, and L. F. Wiggins.

2 : 6-Dimethyl-3-pyridazone has been chlorinated and four different chlorine-containing substances isolated. Two of these have been shown to be 5-chloro- and 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone.

In continuation of studies on pyridazine derivatives obtained from sucrose through lævulic acid as the essential intermediate, we have studied the chlorination of 2 : 6-dimethyl-3-pyridazone (I). This was prepared from lævulic acid by conversion into 6-methyl-3-pyridazone (see Part I, Overend and Wiggins, *J.*, 1947, 239) followed by methylation. That the entering methyl group was attached to the nitrogen atom at position 2 was proved by synthesis of dimethylpyridazone from methylhydrazine and lævulic acid (Overend and Wiggins, unpublished work). It was envisaged that chlorination of 2 : 6-dimethyl-3-pyridazone might permit the introduction of new substituent groups at the unsubstituted carbon atoms remaining in the pyridazone nucleus. Particularly, the amino-derivatives, 4-amino- (II) and 4 : 5-diamino-2 : 6-dimethyl-3-pyridazone (III) were required for certain pharmacological tests and also for the preparation of sulphanilamido-derivatives, since preliminary chemotherapeutic trials have shown that several sulphanilamido-pyridazone and -pyridazine derivatives show marked promise as bacteriostatic agents.



Chlorination of 2 : 6-dimethyl-3-pyridazone (I) has already been described by Meyer (D.R.-P. 579,391, 1933), who claimed to have prepared 4-chloro-2 : 6-dimethyl-3-pyridazone (IV) and an unknown dichloro-derivative of 2 : 6-dimethyl-3-pyridazone, for which he gave no constants. These substances were not defined clearly in the patent, nor have they been described subsequently, and no proof of their constitution has been presented hitherto.

In the present work, the chlorination of (I) was found not to proceed in so clear-cut a manner as Meyer (*loc. cit.*) described. It has been found that on treating (I) in the fused state with chlorine in ordinary daylight at 100°, four, and not only two, products were isolated, namely: (*a*) m. p. 80°; (*b*) m. p. 116°; (*c*) m. p. 114—115°; and (*d*) a material of ill-defined melting point, b. p. 220°. The product (*a*) was clearly the same as Meyer's so-called 4-chloro-2 : 6-dimethyl-3-pyridazone, and the mixture of (*b*), (*c*), and (*d*) was what he described as crude dichloro-2 : 6-dimethyl-3-pyridazone. The substances (*c*) and (*d*) have not hitherto been described by other workers. It was also found that these chlorinated products of 2 : 6-dimethyl-3-pyridazone were formed in highly variable yields despite all efforts to ensure constancy of experimental conditions. Three of the four products (*a*, *b*, and *d*) were separated by differences in their

solubility in water, and one of them (*c*) was volatile in steam. It was found that (*d*) and (*a*) were monochloro-derivatives, and (*b*) and (*c*) contained two chlorine atoms in each pyridazone molecule. The constitution of (*a*) and (*b*) is discussed herein; the structure of (*c*) and (*d*) will be dealt with in a later paper.

Oxidation of the dichlorodimethylpyridazone (*b*) with potassium dichromate and sulphuric acid yielded a carboxylic acid still containing both chlorine atoms. This compound was found (see later) to be dichloromethylpyridazonecarboxylic acid. Since an *N*-methyl group would give on oxidation $N{\cdot}CO_2H$ which would be easily decarboxylated to NH, it was more likely to be the 6-methyl that had undergone oxidation to a carboxyl group. Some evidence for the supposition that the 6-methyl group is oxidised in preference to the *N*-methyl group is deduced from the fact that oxidation of 2 : 6-dimethyl-3-pyridazone leads to the formation of 2-methyl-3-pyridazone-6-carboxylic acid (VI). We have been able to allocate a precise structure to this compound (*b*) by the following synthetic approach. Mucochloric acid (VIII), which was obtained by Simonis (*Ber.*, 1899, **32**, 2085) from furfuraldehyde and chlorine, was condensed with methylhydrazine to give a dichloromethylpyridazone which from the method of preparation must be 4 : 5-dichloro-2-methyl-3-pyridazone (IX). The product of oxidation of (*b*) was then decarboxylated and gave, in high yield, a substance identical with (IX). Therefore the carboxylic acid produced by oxidation of (*b*) must be 4 : 5-dichloro-2-methyl-3-pyridazone-6-carboxylic acid (VII). It follows directly that (*b*) itself must be 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone (V).

The monochloro-derivative of 2 : 6-dimethyl-3-pyridazone (*a*) may have any of the structures (IV) or (X—XII). The possible formulæ (XI and XII) can be eliminated, however, because the monochloro-derivative (*a*) has been converted, by chlorination, into 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone in good yield; thus it follows that in (*a*) the chlorine atom must be attached to the pyridazone residue at either C_4 or C_5, and (*a*) is represented by either (IV) or (X). A decision between these two possibilities has been made by a synthetic procedure.

The chlorine atom in the monochloro-derivative (*a*) of 2 : 6-dimethyl-3-pyridazone was replaced by a carboxyl group by treatment with cuprous cyanide–potassium cyanide under pressure. The intermediate copper complex first isolated was decomposed to a carboxylic acid which had m. p. 183—185°, and behaved on potentiometric titration as a monobasic acid of K $1{\cdot}9 \times 10^{-4}$ in aqueous solution. This substance must be either 2 : 6-dimethyl-3-pyridazone-4- (XIII) or -5-carboxylic acid (XIV).

The intermediate copper complex first formed was a green crystalline solid which could be recrystallised from boiling water without decomposition. It dissolved in hot dilute hydrochloric acid without precipitation of cuprous chloride, so that copper is probably in the cupric state. The ratio of pyridazone residues to each copper atom was found by determination of copper to be 3·4 (gravimeteric) and 4·6 (polarographic). Despite the wide discrepancy between these two results it is fairly clear that four pyridazone residues are associated with one copper atom. The precise form in which this association takes place is not yet known, but will be studied. The complex was decomposed with nitric acid to give the carboxylic acid, m. p. 183—185°.

If one of the compounds (XIII) or (XIV) could be synthesised and proved to be identical or otherwise with the carboxylic acid, m. p. 183—185°, obtained from the monochloro-derivative (*a*), the constitution of (*a*) would automatically follow. We have now synthesised 2 : 6-dimethylpyridazone-4-carboxylic acid (XIII) in the following way. Ethyl acetonylmalonate (XV) was condensed with hydrazine to yield ethyl 6-methyl-3-pyridazinone-4-carboxylate (XVI) (Gault and Salomon, *Ann. Chim.*, 1924, **2**, 133). This gave on treatment with bromine in anhydrous acetic acid and by simultaneous de-esterification, *6-methyl-3-pyridazone-4-carboxylic acid* (XVII). The experimental conditions used were those found most favourable for the dehydrogenation of 6-methyl-3-pyridazinone to the corresponding pyridazone (Overend and Wiggins, *J.*, 1947, 239). Methylation of (XVII) with methyl iodide and sodium methoxide gave a product which must be 2 : 6-*dimethyl-3-pyridazone-4-carboxylic acid*. [Methylation of 6-methyl-3-pyridazone with these reagents has been found to yield 2 : 6-dimethylpyridazone (Overend and Wiggins, *loc. cit.*).] It had m. p. 150—153° and behaved as a monobasic carboxylic acid on potentiometric titration (K $1{\cdot}7 \times 10^{-4}$ in 20% aqueous alcohol). It was clearly different from the carboxylic acid, m. p. 183—185°, obtained from the monochloro-derivative (*a*). It follows that the carboxylic acid obtained from (*a*) is 2 : 6-*dimethyl-3-pyridazone-5-carboxylic acid* (XIV). The original monochloro-derivative (*a*) of 2 : 6-dimethyl-3-pyridazone is therefore 5-chloro-2 : 6-dimethyl-3-pyridazone (X).

Both the monochloro-derivative (*a*) and the dichloro-derivative (*b*) of 2 : 6-dimethyl-3-pyridazone showed absorption in the ultra-violet with a maximum at 3060 A. Also the original 2 : 6-dimethyl-3-pyridazone showed absorption with the head of the band in practically the same

position, at 2940 A. This shows that all three compounds have essentially the same type of structure.

An attempt to chlorinate 2 : 6-dimethyl-3-pyridazone with phosphorus pentachloride in a similar way to that in which 2-phenyl-6-methyl-3-pyridazone was converted into 4-chloro-2-phenyl-6-methyl-3-pyridazone (Overend and Wiggins, *J.*, 1947, 549) was not successful. It led to extensive demethylation at the nitrogen atom with formation of 6-methyl-3-pyridazone, and only a very small amount of a chlorine-containing product which has not yet been identified was isolated.

Experimental.

2 : 6-*Dimethyl*-3-*pyridazone*.—(*a*) Anhydrous 6-methyl-3-pyridazone (50 g.) was refluxed for 2 hours with methyl iodide (65 g.) and sodium (10·5 g.) in dry methyl alcohol (500 c.c.). A " drycold " cooled condenser fitted above the water condenser gave a marked improvement in yield. The mixture was evaporated to small bulk, diluted with water, and continuously extracted with ether. The extract was dried ($MgSO_4$), and on evaporation gave 2 : 6-dimethyl-3-pyridazone as a solid residue (40% yield) which distilled at 109—112°/16 mm., and after recrystallisation from ligroin had m. p. 50—51° in agreement with that found by Overend and Wiggins (forthcoming communication). The compound showed absorption at $\lambda_{max.}$ 2940 A. with $\varepsilon_{max.}^{7\cdot48\%}$ *ca.* 2460 in ethyl alcohol.

(*b*) Anhydrous 6-methyl-3-pyridazone (20 g.) was heated in an autoclave at 130° for 3½ hours with methyl iodide (25 g.) and sodium (4·3 g.) dissolved in dry methyl alcohol (200 c.c.). The mixture was diluted with water and evaporated to small bulk, and the residue was extracted with benzene. The extract was dried ($MgSO_4$) and evaporated to an oil which solidified on cooling and after recrystallisation from light petroleum (b. p. 40—60°) had m. p. 50—51°. Yield of 2 : 6-dimethyl-3-pyridazone 9 g. (48%).

(*c*) Anhydrous 6-methyl-3-pyridazone (4·5 g.) was added slowly during 2 hours with stirring to liquid ammonia (200 c.c.) (cooled in " drycold "–alcohol freezing mixture) containing sodium (0·95 g.) and methyl iodide (7 g.). The ammonia was allowed to evaporate and the residue was dissolved in water and extracted with benzene as above. 2 : 6-Dimethyl-3-pyridazone (2·1 g.; 40%) was obtained.

Chlorination of 2 : 6-*Dimethyl*-3-*pyridazone*.—Anhydrous 2 : 6-dimethyl-3-pyridazone (10 g.) was heated on a boiling water-bath and dry chlorine passed in at a rate of 10 l./hour for 1 hour. The crude melt after cooling was triturated with water (50 c.c.) and the insoluble material filtered off.

The filtrate was made strongly alkaline with 5N-sodium hydroxide. The solid 5-*chloro*-2 : 6-*dimethyl*-3-*pyridazone* (*a*) which separated (4·2 g.), m. p. 80°, showed absorption in the ultra-violet at $\lambda_{max.}$ 3060 A. and $\varepsilon_{max.}^{3\cdot22\%}$ *ca.* 3750 in ethyl alcohol (Found : C, 45·1; H, 4·3; N, 17·0. $C_6H_7ON_2Cl$ requires C, 45·4; H, 4·5; N, 17·7%).

The combined insoluble fraction from 7 chlorination experiments (28·5 g.) was extracted with boiling water (1 l.). The clear liquor was decanted from the insoluble oil. On cooling, crystals of 4 : 5-*dichloro*-2 : 6-*dimethyl*-3-*pyridazone* (*b*) (17·3 g.) were deposited, m. p. 116·5°, showing absorption band maximum at $\lambda_{max.}$ 3060 A. with $\varepsilon_{max.}^{4\cdot0\%}$ *ca.* 4000 (Found : C, 37·9; H, 3·2; N, 13·9. $C_6H_6ON_2Cl_2$ requires C, 37·3; H, 3·1; N, 14·5%).

The insoluble oily material gave on steam distillation crystals (1 g.) of a *dichloro*-derivative of 2 : 6-dimethyl-3-pyridazone, m. p. 114—115° (Found : C, 37·3; H, 3·2; N, 14·5%).

The filtrate from the 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone was extracted with chloroform, and the dried extract evaporated to an oil which solidified on cooling. This was a monochloro-derivative of 2 : 6-dimethyl-3-pyridazone (*d*) and was purified by distillation, b. p. 220°. It had, however, no definite m. p. and was probably a mixture of isomeric monochloro-compounds (Found : Cl, 22·7. Calc. for $C_6H_7ON_2Cl$: Cl, 22·4%).

Chlorination of 5-*Chloro*-2 : 6-*dimethyl*-3-*pyridazone*.—5-Chloro-2 : 6-dimethyl-3-pyridazone (2 g.) was fused at 100° and dry chlorine passed in at a rate of 5 l./hour for 1 hour. The melt, which solidified on cooling, gave, on crystallisation from water, 1·2 g. of material, m. p. 116°, alone or in admixture with 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone.

2 : 6-*Dimethyl*-3-*pyridazone*-5-*carboxylic Acid*.—5-Chloro-2 : 6-dimethyl-3-pyridazone (2 g.), potassium cyanide (2 g.), and cuprous cyanide (0·5 g.) were heated with ethyl alcohol (10 c.c.) and water at 200° in a sealed tube for 5½ hours. The mixture was acidified with sulphuric acid and continuously extracted with ether. The extract was dried ($MgSO_4$) and evaporated to a solid residue (50 mg.) which recrystallised from water as green needles, and had m. p. 317° (decomp.). An ash determination (as CuO) showed it to contain 10·0% of Cu, and a polarographic estimation gave 8·3% of Cu. The former indicated the presence of 3·4 units and the latter 4·6 units of the pyridazone molecule per copper atom. Treatment of the complex with dilute hydrochloric acid gave a clear green solution. No cuprous chloride was precipitated, indicating that the copper was present in the cupric state. After being boiled with dilute nitric acid the copper complex deposited colourless crystals of 2 : 6-*dimethyl*-3-*pyridazone*-5-*carboxylic acid*, m. p. 183—185°, which behaved as a monobasic carboxylic acid on potentiometric titration (in water) having K 1·9 × 10^{-4} (Found : C, 49·6; H, 4·54; equiv., 164. $C_7H_8O_3N_2$ requires C, 50·0; H, 4·77%; equiv., 168).

6-*Methyl*-3-*pyridazone*-4-*carboxylic Acid*.—Ethyl 6-methyl-3-pyridazinone-4-carboxylate (Gault and Salomon, *loc. cit.*) (1·1 g.) was dissolved in dry acetic acid (20 c.c.). Bromine (0·9 g.) was added slowly and the mixture allowed to stand for 24 hours. Water was added, and the solution evaporated to a syrup. Water was repeatedly distilled over this to remove as much hydrogen bromide as possible. The residue deposited some crystals of 6-*methyl*-3-*pyridazone*-4-*carboxylic acid* which were separated and recrystallised from water, m. p. 182—183° (Found : C, 47·1; H, 4·1; N, 18·3; equiv., 158. $C_6H_6O_3N_2$ requires C, 46·8; H, 3·9; N, 18·2%; equiv., 154). Yield 0·33 g.

The acid (0·2 g.) was refluxed with 2% methyl-alcoholic hydrogen chloride (10 c.c.) for 6 hours. The solution was neutralised with lead carbonate, filtered, and evaporated to dryness. The *methyl* ester,

recrystallised from water, had m. p. 161—162° (Found: N, 16·3. $C_7H_8O_3N_2$ requires N, 16·6%). Yield 40 mg.

2 : 6-*Dimethyl*-3-*pyridazone*-4-*carboxylic Acid*.—6-Methyl-3-pyridazone-4-carboxylic acid (103 mg.) was dissolved in dry methyl alcohol (3 c.c.) containing sodium (14·2 mg., 2 mols.) and methyl iodide (85 mg.). The solution was refluxed for 2 hours and then poured into water and acidified with hydrochloric acid. Extraction with ether gave 2 : 6-*dimethyl*-3-*pyridazone*-4-*carboxylic acid*; K, $1·7 \times 10^{-4}$ (in 20% aqueous alcohol), m. p. 150—153° (Found: N, 16·6; equiv., 167. $C_7H_8O_3N_2$ requires N, 16·6%; equiv., 168).

2-*Methyl*-3-*pyridazone*-6-*carboxylic Acid*.—Finely powdered potassium dichromate (28·40 g., 20% excess) was added slowly in portions, with constant stirring, to 2 : 6-dimethyl-3-pyridazone (5·0 g.) dissolved in concentrated sulphuric acid (50 c.c.). The temperature was at first kept at *ca.* 20°, but when about half of the dichromate had been added the water-bath was removed, and the mixture allowed to warm slowly until the reaction commenced as indicated by the development of a green coloration. The cold water-bath was then replaced, and the addition of dichromate continued. Thereafter the temperature was raised to 70° for 1 hour. After cooling, the dark green viscous liquid was extracted with ether, the ethereal extract was washed with water and dried ($MgSO_4$), and the ether was evaporated. The white crystalline residue recrystallised from water formed feathery needles (0·2 g.), m. p. 239°. After some time the mixture of residues and washings deposited crystals which were collected and recrystallised from water, giving needles (0·5 g.), m. p. 239° alone or in admixture with the product from the ether extract. The 2-*methyl*-3-*pyridazone*-6-*carboxylic acid* had K, $6·3 \times 10^{-4}$ (Found: C, 46·3; H, 4·0; N, 18·3; equiv., 157·7. $C_6H_6O_3N_2$ requires C, 46·7; H, 3·9; N, 18·2%; equiv., 154).

The acid (0·2 g.) was heated on a water-bath under reflux, with 2% methyl-alcoholic hydrogen chloride for 6 hours. After neutralisation with barium carbonate, filtration, and evaporation of the filtrate under reduced pressure, the residue was extracted with chloroform. Evaporation of the chloroform extract and recrystallisation of the residue from ligroin (b. p. 60—80°) gave long needles of *methyl* 2-*methyl*-3-*pyridazone*-6-*carboxylate* (0·2 g.), m. p. 103°, alone or in admixture with the compound obtained below by methylation of methyl 3-pyridazone-6-carboxylate (Found: C, 49·8; H, 4·76. $C_7H_8O_3N_2$ requires C, 50·0; H, 4·76%).

Methyl 3-*Pyridazone*-6-*carboxylate*.—3-Pyridazone-6-carboxylic acid (see following paper) (6·0 g.) was heated under reflux for 6 hours with 2% methyl-alcoholic hydrogen chloride (100 c.c.). After the mixture had been kept overnight fine needles separated which, on filtration and recrystallisation from methyl alcohol, gave *methyl* 3-*pyridazone*-6-*carboxylate* (6·45 g.; 98%), m. p. 188° (Found: C, 47·0; H, 3·8; N, 18·7. $C_6H_6O_3N_2$ requires C, 46·7; H, 3·9; N, 18·2%).

Methyl 2-*Methyl*-3-*pyridazone*-6-*carboxylate*.—To methyl 3-pyridazone-6-carboxylate (4·0 g.) in dry methyl alcohol was added a dry methyl-alcoholic solution of sodium methoxide (1·4 g.) and methyl iodide (5 c.c.). The mixture was heated under reflux on a water-bath for 1 hour. The yellow solution was evaporated nearly to dryness under reduced pressure, water (about 20 c.c.) was added, and the mixture extracted with benzene. The benzene extract was dried ($MgSO_4$) and the solvent removed. A white crystalline solid remained which, recrystallised from ligroin (b. p. 60—80°), formed long needles of methyl 2-methyl-3-pyridazone-6-carboxylate (2·75 g.; 63·5%), m. p. 103°.

5-*Chloro*-2-*methyl*-3-*pyridazone*-6-*carboxylic Acid*.—2 : 6-Dimethyl-5-chloro-3-pyridazone (2·5 g.) was dissolved in concentrated sulphuric acid, and finely powdered potassium dichromate (11·16 g., 2·2 mols.) was added slowly at 0° with continuous stirring. When nearly half of the dichromate had been added the ice-bath was removed and the flask allowed to warm gradually. When the reaction began to progress too rapidly, the ice-bath was replaced and the rest of the dichromate added. The temperature was then raised to 60° for 1 hour, and the mixture cooled and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallised several times from acetone–ligroin (b. p. 40—60°), and was obtained in feathery needles (0·15 g.), m. p. 188°. The 5-*chloro*-2-*methyl*-3-*pyridazone*-6-*carboxylic acid* had K, $2·2 \times 10^{-3}$ (Found: C, 38·2; H, 2·8; N, 15·1; Cl, 19·7; equiv., 188·8. $C_6H_5O_3N_2Cl$ requires C, 38·2; H, 2·6; N, 14·9; Cl, 18·8%; equiv., 188·5).

4 : 5-*Dichloro*-2-*methyl*-3-*pyridazone* 6-*Carboxylic Acid*.—To 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone (2·5 g.) in concentrated sulphuric acid (15 c.c.) finely powdered potassium dichromate (7·7 g.) was slowly added, with continuous stirring. The reaction was allowed to proceed at room temperature with periodic cooling to prevent the reaction from becoming too vigorous. The mixture was then cooled to 0°, poured on crushed ice, and exhaustively extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. Repeated recrystallisation of the residue from water gave 4 : 5-*dichloro*-2-*methyl*-3-*pyridazone*-6-*carboxylic acid* (0·5 g.); this had K, $2·5 \times 10^{-3}$, and m. p. 203—204° (Found: C, 32·4; H, 2·2; N, 12·4; Cl, 32·7; equiv., 228·0. $C_6H_4O_3N_2Cl_2$ requires C, 32·2; H, 1·8; N, 12·6; Cl, 31·8%; equiv., 223·0).

4 : 5-*Dichloro*-2-*methyl*-3-*pyridazone*.—(*a*) 4 : 5-Dichloro-2-methyl-3-pyridazone-6-carboxylic acid (0·5 g.) was heated to above its melting point; carbon dioxide was evolved and the product distilled and immediately solidified. Recrystallisation from aqueous alcohol gave 4 : 5-dichloro-2-methyl-3-pyridazone in quantitative yield, m. p. 90—91° (alone or in admixture with the product obtained in (*b*) below).

(*b*) Methylhydrazine sulphate (0·85 g.) was dissolved in water (10 c.c.) containing sodium hydroxide (0·24 g., 1 mol.), and mucochloric acid (1·0 g.), prepared according to the method of Simonis (*loc. cit.*), in ethyl alcohol (10 c.c.) was then added and the solution refluxed for 2 hours. On cooling, crystals of 4 : 5-*dichloro*-2-*methyl*-3-*pyridazone* separated (0·95 g.; 97%) and were collected and recrystallised from aqueous alcohol, m. p. 91° (Found: C, 33·4; H, 2·2; N, 15·6. $C_5H_4ON_2Cl_2$ requires C, 33·6; H, 2·2; N, 15·7%).

The authors gratefully acknowledge the support of the Colonial Products Research Council during this investigation.

THE A.E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15.

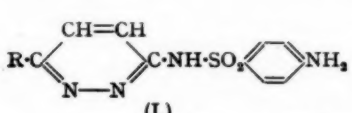
[*Received, February 16th*, 1948.]

445. *The Conversion of Sucrose into Pyridazine Derivatives. Part IV. Further Sulphanilamides derived from 6-Methyl-3-pyridazone.*

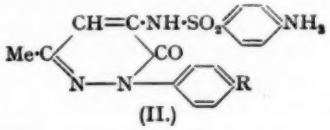
By R. F. Homer, Hilda Gregory, W. G. Overend, and L. F. Wiggins.

A method of synthesis of 3-sulphanilamidopyridazine from the 6-methyl-3-pyridazone obtained from lævulic acid (Overend and Wiggins, *J.*, 1947, 239) is described. The bacteriostatic activity of this compound compared with that of 3-sulphanilamido-6-methylpyridazine is discussed. *5-Sulphanilamido-2 : 6-dimethyl-3-pyridazone* has been obtained; this, however, has no marked bacteriostatic activity *in vitro*.

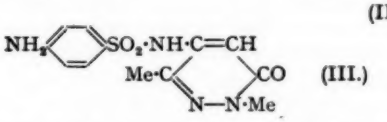
Parts I and II (*J.*, 1947, 239, 549) of this series described several sulphanilamides, containing the pyridazine or pyridazone nucleus, which had been obtained using lævulic acid as the essential intermediate. 3-Sulphanilamido-6-methylpyridazine (I; R = Me) (Part I) was shown to possess a very high bacteriostatic activity *in vitro* against various micro-organisms. 4-Sulphanilamido-2-phenyl-6-methyl-3-pyridazone (II; R = H) (Part II) also derived from lævulic acid through its phenylhydrazone, also possessed considerable activity in routine bacteriostatic tests, but this was less marked than that shown by (I; R = Me) or sulphathiazole, although, despite the presence of the phenyl residue, it possessed better solubility properties than the latter compound. 4-Sulphanilamido-2-*p*-nitrophenyl-6-methyl-3-pyridazone (II; R = NO_2) was also made, but this was too sparingly soluble to be of use.



(I.)



(II.)



(III.)

The effect of (I; R = Me) in mice has now been investigated by Dr. A. T. Fuller of the National Institute for Medical Research. Dr. Fuller's tests indicate that (I; R = Me) is better than sulphanilamide against *Streptococcus hæmolyticus* (Richards) infection in mice. Furthermore, although it failed to protect mice against 100 lethal doses of staphylococcus, it was more efficient than sulphathiazole when used against 5. In an examination of its effect, compared with that of sulphathiazole, against *Clostridium welchii* in guinea pigs, it was found that there was little difference in the effectiveness of the two drugs, though with (I; R = Me) the occurrence of *Cl. welchii* at the injection site in the survivors was less than that occurring when sulphathiazole was used.

Since these results seemed promising it was thought worth while to prepare other sulphanilamide derivatives of pyridazine and 3-pyridazone, and *5-sulphanilamido-2 : 6-dimethyl-3-pyridazone* (III) and 3-sulphanilamidopyridazine (I; R = H) are now described; the latter, first made by Anderson, Faith, Marson, Roblin, and Winneck (*J. Amer. Chem. Soc.*, 1942, **64**, 2902), has now been made from lævulic acid.

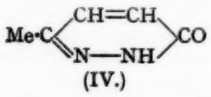
5-Sulphanilamido-2 : 6-dimethyl-3-pyridazone has been obtained in the following way.

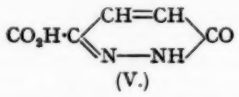
5-Chloro-2 : 6-dimethyl-3-pyridazone on treatment with aqueous ammonia under pressure readily gave *5-amino-2 : 6-dimethyl-3-pyridazone* characterised as the *hydrochloride*, *picrate*, and *acetyl* derivative. This amine with *p*-acetamidobenzenesulphonyl chloride afforded *5-(p-acetamidobenzenesulphonamido)-2 : 6-dimethyl-3-pyridazone*, which on hydrolysis yielded *5-sulphanilamido-2 : 6-dimethyl-3-pyridazone* (III). This formed a characteristic *monohydrochloride*. The behaviour of (III) in bacteriostatic tests is shown below, where it is seen that although it does possess some activity, this is much less than that shown by sulphathiazole.

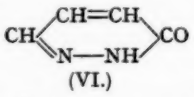
	Strep. hæmolyticus.		*Staph. aureus.*		*B. coli.*	
Compound.	Blood medium.	Broth medium.	Synth. medium.	Broth medium.	Synth. medium.	Broth medium.
5-Sulphanilamido-2 : 6-dimethyl-3-pyridazone	2	10	500	1000	2	50
Sulphathiazole	0·2	—	1	—	0·05	5

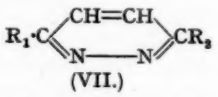
The figures represent mg. of compound/100 c.c. of solution necessary to prevent growth of organisms.

3-Sulphanilamidopyridazine (I; R = H) was first obtained by Anderson *et al.* (*loc. cit.*) through the 3-chloropyridazine obtained by Gabriel (*Ber.*, **1909**, **42**, 655) from 2-ketoglutaric acid by condensation with hydrazine. The product, 3-pyridazinone-6-carboxylic acid was dehydrogenated to form 3-pyridazone-6-carboxylic acid which was then decarboxylated to 3-pyridazone. This with phosphoryl chloride gave 3-chloropyridazine. This compound has now been obtained from lævulic acid in the following way. 6-Methyl-3-pyridazone (IV) is readily made from lævulic acid (Part I, *loc. cit.*). Now it has been found that the methyl group in this compound can be easily oxidised by means of potassium dichromate and sulphuric acid to give, in 70% yield, 3-pyridazone-6-carboxylic acid (V), identical with Gabriel's compound (*loc. cit.*). The dichromate–sulphuric acid method of oxidation was far superior to the nitric acid oxidation which Paal and Dencks (*Ber.*, **1903**, **36**, 491) used to oxidize 3-phenyl-6-methylpyridazine to 3-phenylpyridazine-6-carboxylic acid. Under Paal and Denck's conditions only minute yields of (V) were obtained from 6-methylpyridazone.


(IV.)


(V.)


(VI.)


(VII.)

(V) was readily transformed into the characteristic *ethyl* ester and the 6-*carbamyl* derivative. It was readily decarboxylated at its melting point, to yield 3-pyridazone (VI) in 88% yield. Treatment of this with phosphoryl chloride gave 3-chloropyridazine (VII; R_1 = H, R_2 = Cl) in high yield. This compound was not very stable since it darkened and liquefied even on being kept at 0° in a vacuum. Its hydrochloride was also unstable in air. A possible alternative method of preparation of (VII; R_1 = H, R_2 = Cl) was by oxidation of 3-chloro-6-methylpyridazine (VII; R_1 = Me, R_2 = Cl) followed by decarboxylation of the 3-*chloropyridazine*-6-*carboxylic acid* (VII; R_1 = CO_2H, R_2 = Cl) produced. Attempts to decarboxylate 3-chloropyridazine-6-carboxylic acid were abandoned when the extreme instability of 3-chloropyridazine even at low temperatures and under anhydrous conditions was confirmed. Some aspects of the preparation and properties of the acid are, however, of interest. Attempts to oxidise 3-chloro-6-methylpyridazine with nitric acid according to the method of Paal and Dencks (*loc. cit.*) failed, and led only to removal of the chlorine atom with formation of 6-methyl-3-pyridazone. Oxidation with potassium dichromate and sulphuric acid, however, afforded the 6-carboxylic acid in 65% yield. The acid was identical with the product of chlorination of 3-pyridazone-6-carboxylic acid with phosphoryl chloride, though the yield of the 3-chloro-compound by the latter procedure was only 38%. The chlorine atom in this compound was extremely labile and was completely removed by refluxing with 2% ethyl-alcoholic hydrogen chloride, which gave ethyl pyridazone-6-carboxylate only.

Treatment of 3-chloropyridazine with methyl-alcoholic ammonia under pressure resulted in the formation of 3-aminopyridazine (VII; R = H, R_2 = NH_2), identical with that described by Anderson (*loc. cit.*), in good yield. This on treatment with *p*-acetamidobenzenesulphonyl chloride gave 3-(p-*acetamidobenzenesulphonamido*)*pyridazine*, which, on hydrolysis with either dilute alkali or acid, afforded 3-sulphanilamidopyridazine, m. p. 175°. Anderson *et al.* (*loc. cit.*) record m. p. 189—190° for this compound. We were unable to raise the melting point of our compound to this value even by repeated recrystallisation.

The American authors first made this compound and reported that, although it possessed a remarkably high activity in bacteriostatic tests against *Esch. coli* yet against streptococcal and pneumococcal infection in mice it was practically inactive. This, in view of the high activity of 3-sulphanilamido-6-methylpyridazine *in vitro* and *in vivo*, appeared very remarkable, and one of the reasons for the preparation of 3-sulphanilamidopyridazine was to enable a biological re-examination of it to be made. Dr. A. T. Fuller has tested this compound against *Strep. hæmolyticus* (Richards) in mice and he finds that it is more active than sulphanilamide itself when given orally, but is inactive when given intraperitoneally. Although Anderson *et al.* gave no details of their method of testing 3-sulphanilamidopyridazine, the inference is that they did so intraperitoneally, which would account for their statement that this substance was inactive *in vivo*.

Experimental.

Treatment of 5-Chloro-2 : 6-dimethyl-3-pyridazone with Ammonia.—5-Chloro-2 : 6-dimethyl-3-pyridazone (Part III, preceding paper) (7·8 g.) was dissolved in aqueous ammonia (*d*, 0·88) (750 c.c.) and heated at 160° for 60 hours in an autoclave. The mixture was evaporated to dryness under reduced pressure, and the residue extracted with chloroform in an atmosphere of nitrogen. The extract was dried ($MgSO_4$) and evaporated to a thick syrup which crystallised on trituration with acetone. The

crude material, recrystallised from acetone, gave *5-amino-2 : 6-dimethyl-3-pyridazone* (4·0 g.; 58%), m. p. 163° (Found : C, 51·4; H, 6·2; N, 29·7. $C_6H_9ON_3$ requires C, 51·8; H, 6·4; N, 30·2%).

A small quantity of the amine was dissolved in absolute alcohol and the solution saturated with hydrogen chloride. White crystals of the *hydrochloride* separated, and after recrystallisation from absolute alcohol containing a little hydrogen chloride had m. p. *ca.* 245° (decomp.) (Found : C, 41·6; H, 5·8. $C_6H_9ON_3,HCl$ requires C, 41·2; H, 5·7%). The amine (0·5 g.) was dissolved in a little water, and picric acid (1 mol.) dissolved in alcohol added. The precipitated *picrate* was collected and recrystallised from water to form yellow needles (0·06 g.), m. p. 130° (Found : N, 23·2. $C_{12}H_{11}O_8N_6$ requires N, 22·8%).

The amine (0·6 g.) was refluxed with fused sodium acetate (3 g.) and acetic anhydride (20 c.c.) for ½ hour. The mixture was poured into water, neutralised with sodium carbonate, and extracted with chloroform. The dried ($MgSO_4$) extract was evaporated to dryness; the crude *acetyl* derivative recrystallised from water in colourless needles (0·4 g.), m. p. 227° (60%) (Found : C, 53·3; H, 6·1; N, 23·9. $C_8H_{11}O_2N_3$ requires C, 53·0; H, 6·0; N, 23·2%).

5-(p-Acetamidobenzenesulphonamido)-2 : 6-dimethyl-3-pyridazone.—The amine (5·0 g.) and *p*-acetamidobenzenesulphonyl chloride (8·5 g.) were separately dissolved in dry pyridine, the solutions mixed, and the mixture kept at 40° for 1 hour. It was then poured into water, sodium hydroxide (1·45 g., 1 mol) added, and the solution distilled with much water to remove pyridine. A yellowish solid separated, and was filtered off and recrystallised from alcohol–acetic acid. *5-(p-Acetamidobenzenesulphonamido)-2 : 6-dimethyl-3-pyridazone* (2·2 g.) separated as pink microcrystals, m. p. 263° (Found : C, 49·8; H, 4·8. $C_{14}H_{16}O_4N_4S$ requires C, 50·0; H, 4·8%).

5-Sulphanilamido-2 : 6-dimethyl-3-pyridazone.—The acetyl derivative (1·5 g.) was refluxed with 10% aqueous sodium hydroxide (20 c.c.) for ¾ hour. On being neutralised with hydrochloric acid the solution deposited a yellow solid which was collected and recrystallised from aqueous alcohol, forming yellow needles of *5-sulphanilamido-2 : 6-dimethyl-3-pyridazone monohydrate* (1·2 g.), m. p. 113—123° (Found : C, 46·4; H, 5·2. $C_{12}H_{14}O_3N_4S,H_2O$ requires C, 46·2; H, 5·15%). The *anhydrous* compound had m. p. 207° (Found : N, 19·4. $C_{12}H_{14}O_3N_4S$ requires N, 19·1%).

The sulphanilamido-compound (0·05 g.) was shaken with acetic anhydride (3 c.c.) and 5N-acetic acid (3 c.c.). After a few minutes, crystals of the acetyl derivative (0·05 g.) separated, m. p. 262° alone or in admixture with an authentic specimen.

The sulphanilamide monohydrate (50 mg.) was dissolved in dry methyl alcohol and the solution was saturated with hydrogen chloride. On addition of ether, a yellowish powder was precipitated, which, when recrystallised from methyl alcohol containing a little hydrogen chloride, formed pale yellow needles of the *hydrochloride monohydrate* (40 mg.), m. p. 180° (decomp.) (Found : C, 41·1; H, 4·8; N, 16·2. $C_{12}H_{14}O_3N_4S,HCl,H_2O$ requires C, 41·4; H, 4·9; N, 16·1%).

Oxidation of 6-Methyl-3-pyridazone.—(a) *By dilute nitric acid.* 6-Methyl-3-pyridazone (3·0 g.) was heated with nitric acid (10%; 15 c.c.) for 5 hours at 160°. On cooling, crystals separated which were recrystallised from water, giving 3-pyridazone-6-carboxylic acid monohydrate (0·05 g.), m. p. 257°. Gabriel (*loc. cit.*) gives the same m. p. (Found : C, 38·2; H, 3·5; N, 17·8. Calc. for $C_5H_4O_3N_2,H_2O$: C, 38·0; H, 3·8; N, 17·7%). The mother liquors were evaporated to dryness; the residue, recrystallised from water, gave 6-methyl-3-pyridazone (0·015 g.), m. p. 122—123° alone or in admixture with starting material.

(b) *By concentrated nitric acid.* 6-Methyl-3-pyridazone (1·0 g.) was heated with concentrated nitric acid (20 c.c.) in an evaporating basin on a water-bath. Complete evaporation of the acid and recrystallisation of the residue from water gave 100% recovery of the unchanged starting material.

(c) *By potassium dichromate and concentrated sulphuric acid.* To a mechanically stirred solution of 6-methyl-3-pyridazone (5·0 g.) in concentrated sulphuric acid (50 c.c.) potassium dichromate (13·4 g.; 1 mol.) was added in small quantities as a finely ground powder. When the reaction started, as indicated by the development of a green coloration, the flask was cooled in cold water before the addition of potassium dichromate was continued. After the addition was completed, stirring was continued for a further 2 hours, then the viscous green mixture was poured on crushed ice. The colourlesscrystalline powder which separated was collected, washed with alcohol and ether, then recrystallised from hot water giving needles of 3-pyridazone-6-carboxylic acid monohydrate (4·35 g.; 68·4%), m. p. 257°. The results of further experiments carried out under slightly varied conditions are tabulated below.

6-Methyl-3-pyridazone, g.	$K_2Cr_2O_7$, g.	H_2SO_4, c.c.	Temp.	Yield. G.	Yield. %
5	13·4 (1 mol.)	50	40°	4·31	68·0
5	13·4 ,,	50	50	4·28	68·0
5	13·4 ,,	30	30—50	4·2	67·5
5	16·08 (1·2 mol.)	50	30—50	4·62	72·5
50	160·8 ,,	500	30—50	46·15	72·4

Ethyl 3-pyridazone-6-carboxylate. 3-Pyridazone-6-carboxylic acid (2·0 g.) was heated under reflux with 2% ethyl-alcoholic hydrogen chloride for 6 hours on a water-bath. The mixture was thereafter neutralised with lead carbonate and filtered, and the filtrate evaporated to dryness under reduced pressure. Recrystallisation of the residue from hot water gave glistening white flakes of *ethyl 3-pyridazone-6-carboxylate monohydrate* (2·0 g.; 84%), m. p. 102° (Found : C, 45·5; H, 5·2; N, 15·4. $C_7H_8O_3N_2,H_2O$ requires C, 45·2; H, 5·4; N, 15·1%). The anhydrous *ester* had m. p. 122° (Found : C, 50·2; H, 4·7; N, 16·0. $C_7H_8O_3N_2$ requires C, 50·0; H, 4·8; N, 16·6%).

6-Carbamyl-3-pyridazone. A solution of ethyl 3-pyridazone-6-carboxylate (0·3 g.) in ethyl alcohol was saturated with ammonia at 0° and the solution kept at 0° overnight. Crystals separated which were collected, and after being recrystallised from water gave *6-carbamyl-3-pyridazone*, m. p. 304° (decomp.) (Found : C, 43·3; H, 3·9; N, 30·5. $C_5H_5O_2N_3$ requires C, 43·2; H, 3·6; N, 30·2%).

Oxidation of 3-Chloro-6-methylpyridazine.—(*a*) 3-Chloro-6-methylpyridazine (5 g.) (Part I, *loc. cit.*) and 5% nitric acid (150 c.c.) were heated at 160° for 5 hours in a sealed tube. After cooling, the solution was evaporated to dryness; the syrup remaining solidified on addition of water. The solid after recrystallisation from water had m. p. 124—125° alone or in admixture with 6-methyl-3-pyridazone monohydrate. Yield 3·6 g.

(*b*) To a mechanically stirred solution of 3-chloro-6-methylpyridazine (1·8 g.) in concentrated sulphuric acid (10 c.c.), finely powdered potassium dichromate (5·0 g., 20% excess) was added slowly, the temperature being kept below 50°. When the addition was complete, stirring was continued for a further 2 hours at 50°. The oxidation was still not complete, as indicated by the yellowish-green coloration. Thereafter the mixture was heated for a further 2 hours on a boiling water-bath. The viscous, dark green liquid was cooled and added to crushed ice, and the solution extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporated to dryness, and the residue recrystallised from water, giving *3-chloropyridazine-6-carboxylic acid* (1·45 g.; 65·3%), m. p. 146° (Found: C, 37·5; H, 2·2; N, 17·1. $C_5H_3O_2N_2Cl$ requires C, 37·8; H, 1·9; N, 17·6%).

Chlorination of 3-Pyridazone-6-carboxylic Acid.—3-Pyridazone-6-carboxylic acid (3·0 g.) was heated under reflux with phosphoryl chloride (50 c.c.) for 0·5 hour. Most of the excess of phosphoryl chloride was removed under reduced pressure, crushed ice added, and the mixture extracted with ether. The etheral extract was dried ($MgSO_4$) and evaporated to a colourless crystalline solid which was recrystallised from water, giving 3-chloropyridazine-6-carboxylic acid (1·25 g.; 38·0%), m. p. 146° alone or in admixture with the product obtained by oxidation of 3-chloro-6-methylpyridazine.

3-Chloropyridazine-6-carboxylic acid (0·85 g.) was heated under reflux with 2% ethyl-alcoholic hydrogen chloride (40 c.c.) for 6 hours. The resulting solution was neutralised with barium carbonate and filtered, and the filtrate evaporated to dryness. The residue recrystallised from water in rosettes of needles (0·53 g.; 59%), m. p. 121—122° alone or in admixture with ethyl pyridazone-6-carboxylate (Found: N, 16·3. Calc. for $C_7H_8O_3N_2$: N, 16·6%).

3-Pyridazone.—Anhydrous 3-pyridazone-6-carboxylic acid (10·0 g.) was heated gently in a distilling flask until, after fusion of the crystalline mass, the evolution of carbon dioxide subsided. On being heated more strongly, the crude product distilled and solidified in long needles. After repetition of the distillation, followed by recrystallisation of the product from acetone–ethyl alcohol–ligroin, long needles of 3-pyridazone (6·0 g.; 88·0%), m. p. 103° (cf. Gabriel, *loc. cit.*), separated.

3-Chloropyridazine.—Phosphoryl chloride (10 c.c.) was added slowly to 3-pyridazone (3·0 g.). When the vigorous reaction which immediately ensued had slowed down, the mixture was heated on a water-bath for 2 hours at 67°. The excess of phosphoryl chloride was removed under reduced pressure, and the dark brown residue poured on crushed ice. The resulting solution was neutralised with sodium carbonate and extracted with ether, and the ethereal extract dried ($MgSO_4$). Evaporation of the ether at 0° under reduced pressure gave a white crystalline residue, which on careful recrystallisation from ether–ligroin (b. p. 40—60°) gave shiny flakes of 3-chloropyridazine (2·56 g.; 70·8%), m. p. 29° (cf. Gabriel, *loc. cit.*). These quickly decomposed even when kept in a vacuum desiccator at 0°. The hydrochloride was obtained by dissolving the base (0·1 g.) in anhydrous ethyl alcohol and saturating the solution with dry hydrogen chloride at 0°. Crystals, m. p. 122°, separated, but these decomposed too quickly for analytical results to be obtained.

3-Aminopyridazine.—3-Chloropyridazine (15 g.) was heated with methyl alcohol (750 c.c.) saturated with ammonia at 0° in an autoclave at 175° for 2 days. The dark brown solution thereby obtained was filtered and evaporated to dryness under reduced pressure in an atmosphere of nitrogen. The residue was extracted several times with hot ethyl acetate, and the crystals which separated on cooling were collected. Evaporation of the ethyl acetate yielded more of this material which was crude 3-aminopyridazine. The residue, insoluble in ethyl acetate, was heated with barium hydroxide (20 g.) in water (300 c.c.) for 1 hour in an atmosphere of nitrogen, and the mixture thereafter evaporated to dryness and extracted with ethyl acetate. A further crop of crystals was obtained from this extract. Recrystallisation of the total crude product gave 3-aminopyridazine (8·1 g.; 65%), m. p. 169—170° (Found: C, 50·8; H, 5·5; N, 43·6. Calc. for $C_4H_5N_3$: C, 50·5; H, 5·3; N, 44·2%).

3-(p-Acetamidobenzenesulphonamido)pyridazine.—A solution of *p*-acetamidobenzenesulphonyl chloride (14·0 g., 2% excess) in dry pyridine (80 c.c.) was added to 3-aminopyridazine (5·0 g.) also dissolved in dry pyridine (*ca.* 200 c.c.). The resulting dark red solution was kept for 24 hours at room temperature, then poured into water containing sodium hydroxide (1 mol.). The mixture was distilled with water until all the pyridine had been removed; a dark brown oil then separated and slowly solidified. Recrystallisation from water gave *3-(p-acetamidobenzenesulphonamido)pyridazine* (9·35 g.; 60·7%), m. p. 106—107° (Found: C, 49·1; H, 4·0. $C_{12}H_{12}O_3N_4S$ requires C, 49·3; H, 4·1%).

Hydrolysis. (*a*) 3-(*p*-Acetamidobenzenesulphonamido)pyridazine (1·35 g.) was heated with 10% sodium hydroxide solution (15 c.c.) on a boiling water-bath for ½ hour, and the resulting solution was neutralised (litmus) with dilute hydrochloric acid. The free base which separated on standing was collected and recrystallised from water to give 3-sulphanilamidopyridazine as yellow crystals (0·6 g.; 52%), m. p. 175°; solubility at room temp., 0·192 mg./100 c.c. of solution. The m. p. was not raised even by 3 further recrystallisations. Anderson *et al.* (*loc. cit.*) give m. p. 189—190° (Found: C, 47·9; H, 4·2; N, 22·7. Calc. for $C_{10}H_{10}O_2N_4S$: C, 48·0; H, 4·0; N, 22·4%).

(*b*) 3-(*p*-Acetamidobenzenesulphonamido)pyridazine (0·5 g.) was heated with 2N-hydrochloric acid (10 c.c.) on a boiling water-bath for 1 hour. Dilute sodium hydroxide was then added until the solution became turbid and an oil separated which gradually solidified. The solid was collected and recrystallised from water, giving 3-sulphanilamidopyridazine (0·26 g.; 60·7%), m. p. 175° alone or in admixture with the product obtained above by alkaline hydrolysis.

The sulphanilamido-compound (0·1 g.) could be reacetylated, by heating it with acetic anhydride (5 c.c.) and sodium acetate (0·2 g.) for 30 minutes, to 3-(*p*-acetamidobenzenesulphonamido)pyridazine, m. p. 106—107° alone or in admixture with the compound obtained by direct condensation of *p*-acetamidobenzenesulphonyl chloride with 3-aminopyridazine.

The authors are grateful to the Colonial Products Research Council for their support, and to Professor Sir Norman Haworth, F.R.S., and Dr. J. L. Simonsen, F.R.S., for their interest. The biological tests were carried out through the courtesy of Sir Charles Harington, F.R.S., Director of Research, National Institute for Medical Research.

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15. [*Received, February 16th,* 1948.]

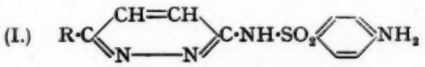
---

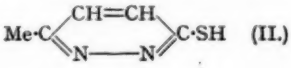
446. *The Conversion of Sucrose into Pyridazine Derivatives. Part V. Experiments on the Synthesis of* 3-*Amino*-6-*methylpyridazine and of its Sulphanilamido-derivative.*

By HILDA GREGORY, W. G. OVEREND, and L. F. WIGGINS.

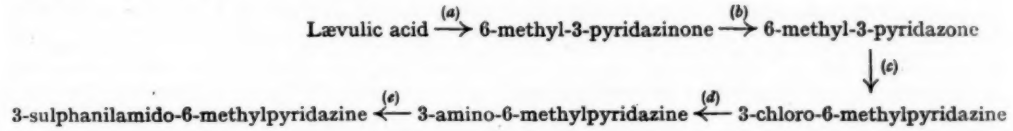
The preparation of 3-mercapto-6-methylpyridazine from both 6-methyl-3-pyridazone and 3-chloro-6-methylpyridazine is described. 6-Methyl-3-pyridazone is found to undergo the Bucherer reaction.

Two sulphanilamidopyridazines have been prepared from lævulic acid and were described in Parts I and IV of this series. These substances were 3-sulphanilamido-6-methylpyridazine (I; R = Me) and 3-sulphanilamidopyridazine (I; R = H). The former compound has been found to have pronounced bacteriostatic power and to possess favourable solubility properties.

(I.) 

 (II.)

Its synthesis was achieved through the following steps:

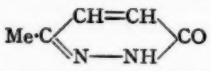
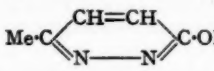


Each of the steps (*a*), (*b*), and (*c*) was readily carried out in > 95% yield. The conversion of 3-chloro-6-methylpyridazine into the corresponding amine was difficult, as would be expected from the aromatic character of the pyridazine ring. The yields usually obtained were of the order of 60%. The final stage in the synthesis was accomplished by the condensation of 3-amino-6-methylpyridazine with *p*-acetamidobenzenesulphonyl chloride followed by hydrolysis of the product. These reactions [step (*e*)], proceeded satisfactorily. Some effort has been made now to improve step (*d*), and, although these efforts have not been successful, some interesting aspects of the chemistry of pyridazone have emerged.

One way in which to improve step (*d*) would be to convert 3-chloro-6-methylpyridazine directly into 3-(*p*-acetamidobenzenesulphonamido)-6-methylpyridazine. Thus, attempts have been made to condense 3-chloro-6-methylpyridazine with *p*-acetamidobenzenesulphonamide. This entirely failed when the reagents were heated in pyridine solution at 150°, but some condensation was effected when the two substances were fused together in the presence of potassium carbonate, although the yield of condensation product was only 10%. It might be envisaged that if 3-*mercapto*-6-*methylpyridazine* (II) could be obtained, the mercapto-group might be more easily replaced than the chlorine atom. Crystalline 3-mercapto-6-methylpyridazine was obtained by heating 3-chloro-6-methylpyridazine with sodium hydrogen sulphide in alcohol at 150°. Alternatively, 6-methyl-3-pyridazone, on treatment with phosphorus pentasulphide, was converted into (II) though in poor (20%) yield. It was also obtained, although in an even smaller yield, when 6-methyl-3-pyridazone was passed over heated aluminium sulphide in a vacuum. The replacement of the mercapto-group by an amino-residue was effected by treatment with methyl-alcoholic ammonia, but 3-amino-6-methylpyridazine was obtained in only very small yield. The replacement did take place, however, at a lower temperature than that obtaining in the case of the 3-chloro-6-methylpyridazine. It was found also that this introduction of an amino-group was as difficult to effect when an ethylthio-group replaced the mercapto-group. 3-*Ethylthio*-6-*methylpyridazine* was obtained on ethylation of the corresponding 3-mercapto-compound with ethyl iodide and sodium hydroxide. Treatment of

this with methyl-alcoholic ammonia gave 3-amino-6-methylpyridazine (18% yield) together with unchanged starting material (80% by weight).

Since 6-methyl-3-pyridazone (III) must exist in equilibrium with its lactim form (IV) there is the possibility that it might undergo the Bucherer reaction, by means of which certain phenolic

(III.)   (IV.)

compounds, particularly naphthols, can be converted into amines. On heating 6-methyl-3-pyridazone with sodium sulphite and ammonia at 240° under pressure, there was isolated, besides unchanged 6-methyl-3-pyridazone, a little 3-amino-6-methylpyridazine. This shows that this pyridazone derivative (IV) does undergo the Bucherer reaction, although the low yield prohibited the attachment of any preparative value to this fact.

Experimental.

3-Mercapto-6-methylpyridazine.—(*a*) 3-Chloro-6-methylpyridazine (2 g.) was heated in a sealed tube at 150° for 3 hours with ethyl alcohol (20 c.c.) saturated with sodium hydrogen sulphide. Crystalline material separated on cooling. This was filtered off and washed with water. Yellow needles remained which, recrystallised from ethyl alcohol–water, formed long yellow needles (1·0 g.; 52·6%) of *3-mercapto-6-methylpyridazine*, m. p. 203·5—205° (decomp.). They exhibited a greenish fluorescence in ultra-violet light (Found: C, 47·8; H, 5·1. $C_5H_6N_2S$ requires C, 47·6; H, 4·8%).

(*b*) 6-Methyl-3-pyridazone (2·5 g.) and phosphorus pentasulphide (6·2 g.) were boiled under reflux in xylene for 3 hours. The hot xylene solution was filtered, and the crystalline solid which separated collected. This, recrystallised from ethyl alcohol–water, formed long yellow needles (0·55 g.; 19·6%), m. p. 203·5—204·5° (decomp.) alone or in admixture with 3-mercapto-6-methylpyridazine.

(*c*) 6-Methyl-3-pyridazone (5·0 g.) was distilled in high vacuum (0·005 mm.) and the vapour was passed over heated aluminium sulphide. A yellow distillate was collected (1·01 g.). This was extracted with hot water. The aqueous extract deposited slightly yellow needles (0·5 g.) which had m. p. 123—125° alone or in admixture with 6-methyl-3-pyridazone monohydrate. The residue, recrystallised from ethyl alcohol–water, formed yellow needles (0·2 g.), m. p. 203—205° (decomp.) alone or in admixture with 3-mercapto-6-methylpyridazine.

Treatment of 3-Mercapto-6-methylpyridazine with Ammonia.—(*a*) The material (0·647 g.) was heated with aqueous ammonia in a sealed tube at 100° for a day. The solution was then evaporated to dryness and the residue extracted with water. The water-insoluble material was unchanged starting material (0·33 g.). The aqueous extract was evaporated to dryness, and then extracted with chloroform. This extract was evaporated, and the residue washed with water to remove last traces of 3-mercapto-6-methylpyridazine. The aqueous extract was evaporated to dryness; the residual solid, recrystallised from water, had m. p. 224° alone or in admixture with 3-amino-6-methylpyridazine. Yield 0·08 g.

3-Ethylthio-6-methylpyridazine.—To 3-mercapto-6-methylpyridazine (1·26 g.) in ethyl alcohol (30 c.c.) was added sodium hydroxide (0·4 g.) in alcohol (5 c.c.), and ethyl iodide (1·56 g.; 1 equiv.) in ethyl alcohol (10 c.c.). The solution was then heated under reflux for 2 hours, and the solvent evaporated under reduced pressure. The residue was extracted with ether; evaporation of the ethereal extract gave a yellow oil which rapidly crystallised. Careful recrystallisation from ether gave colourless needles of *3-ethylthio-6-methylpyridazine*, m. p. 41° (Found: C, 54·4; H, 6·4. $C_7H_{10}N_2S$ requires C, 54·6; H, 6·2%).

Treatment of 3-Ethylthio-6-methylpyridazine with Ammonia.—The compound (1·0 g.) was heated with methyl-alcoholic ammonia (saturated at 0°) in a sealed tube at 160° for 3 days. Evaporation of the solvent gave a semi-crystalline residue. To this, water was added; the oil which separated was extracted with ether, and the residual aqueous portion evaporated to dryness under reduced pressure. Recrystallisation of the residue gave 3-amino-6-methylpyridazine (0·12 g.; 18%), m. p. 222—224° alone or in admixture with an authentic specimen. Evaporation of the ethereal extract gave a yellow oil (0·8 g.) which crystallised and was found to be unchanged starting material.

6-Methyl-3-pyridazone in the Bucherer Reaction.—Sodium sulphite (10·66 g.) was dissolved in water (50 c.c.), 6-methyl-3-pyridazone monohydrate (7·3 g.) added, and the solution made up to 700 c.c. with aqueous ammonia (*d* 0·88). This solution was heated at 240° for 3 days in an autoclave, filtered, and evaporated to dryness. The residue was extracted with acetone, giving an extract (*A*) and a residue (*B*). The extract (*A*) was evaporated to dryness; the residue recrystallised from water (charcoal) in colourless plates (1·0 g.) of β-methyl-3-pyridazone monohydrate, m. p. 123—124°. The residue (*B*) was heated with sodium hydroxide for an hour and then acidified with hydrochloric acid and evaporated to dryness. The solid residue was dried thoroughly and was then extracted first with chloroform [extract (*C*)] and then ethyl alcohol [extract (*D*)]. On removal of the solvent from extract (*C*) a residue was obtained which, recrystallised from water (charcoal), formed colourless needles (0·204 g.), m. p. 123—125° alone or in admixture with 6-methyl-3-pyridazone monohydrate. The extract (*D*) was evaporated to dryness, the residue dissolved in the minimum of water, and a concentrated solution of sodium hydroxide added. Crystals separated which, recrystallised from water, formed colourless rhombs (0·2 g.), m. p. 224° alone or in admixture with 3-amino-6-methylpyridazine.

Attempted Condensation of 3-Chloro-6-methylpyridazine with p-Acetamidobenzenesulphonamide.—(*a*) 3-Chloro-6-methylpyridazine (0·75 g.) and *p*-acetamidobenzenesulphonamide (1·0 g.) were dissolved in dry pyridine (200 c.c.), and the solution heated at 150° in an autoclave for 4 hours. Thereafter the product was concentrated to 20 c.c. and poured into water containing sodium hydroxide (0·23 g.), and unchanged *p*-acetamidobenzenesulphonamide, m. p. 218°, separated. No condensation product could be isolated.

(*b*) 3-Chloro-6-methylpyridazine (0·133 g.), *p*-acetamidobenzenesulphonamide (0·128 g.), and dry potassium carbonate (0·13 g.) were fused together. After being cooled, the mixture was treated with water and the undissolved portion collected. After recrystallisation from acetic acid–water, this product (0·026 g.; 10%) had m. p. 246—247° alone or in admixture with 3-(*p*-acetamidobenzenesulphonamido)-6-methylpyridazine.

The authors gratefully acknowledge the support of the Colonial Products Research Council during this investigation.

THE A.E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15. [*Received, February 16th*, 1948.]

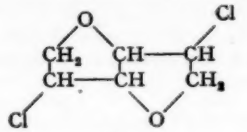
---

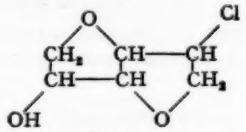
447. *Anhydrides of Polyhydric Alcohols. Part XI. The Action of Phosphorus Tribromide on* 1 : 4-3 : 6-*Dianhydro-mannitol and -sorbitol. Some New Chloro-derivatives of* 1 : 4-3 : 6-*Dianhydrosorbitol.*

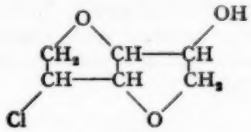
By W. G. OVEREND, R. MONTGOMERY, and L. F. WIGGINS.

In contrast to the corresponding mannitol derivative, the replacement of the hydroxyl groups in 1 : 4-3 : 6-dianhydrosorbitol by halogens is difficult. 2 : 5-*Dichloro* 1 : 4-3 : 6-*dianhydrosorbitol* and a monochloro-derivative, most probably 5-*chloro* 1 : 4-3 : 6-*dianhydrosorbitol*, are described. Treatment of dianhydro-mannitol or -sorbitol with phosphorus tribromide under mild conditions leads not to the introduction of bromine atoms at C_2 and C_5 but to ring cleavage, and derivatives of 1 : 6-dibromo-mannitol and -sorbitol are obtained.

2 : 5-DICHLORO 1 : 4-3 : 6-dianhydromannitol is very readily prepared by treating 1 : 4-3 : 6-dianhydromannitol with thionyl chloride and pyridine (Wiggins, *J.*, 1945, 4). An attempt to prepare 2 : 5-dichloro 1 : 4-3 : 6-dianhydrosorbitol (I), in the same way failed. A sample has, however, been obtained in poor yield by treating 1 : 4-3 : 6-dianhydrosorbitol with thionyl chloride in benzene followed by phosphorus pentachloride. When dianhydrosorbitol was treated with thionyl chloride in xylene followed by thionyl chloride in pyridine, a liquid product was obtained from which there separated a crystalline substance with the composition of a monochloro derivative of dianhydrosorbitol. This must be either 2-chloro 1 : 4-3 : 6-dianhydro-


(I.)

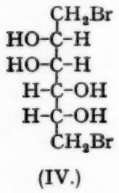

(II.)

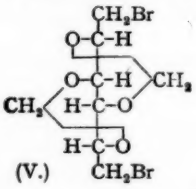

(III.)

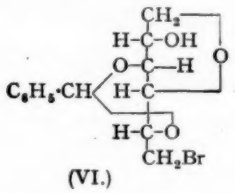
sorbitol (II) or 5-chloro dianhydrosorbitol (III). Since 1 : 4-3 : 6-dianhydromannitol is however, easily chlorinated in positions 2 and 5, and since the only difference between 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol is in the configuration of C_2, it is reasonable to suppose that it is the hydroxyl at this position which is more difficult to replace by chlorine and so remains unsubstituted in the monochloro-derivative of 1 : 4-3 : 6-dianhydrosorbitol. It is therefore tentatively suggested that this substance is 5-*chloro* 1 : 4-3 : 6-*dianhydrosorbitol*. Further work is proceeding in order to prove this.

In view of the stability of 2 : 5-dichloro 1 : 4-3 : 6-dianhydromannitol (see Wiggins, *loc. cit.*) and of the fact that it has been found difficult to make the corresponding sorbitol derivative, an attempt was made to introduce bromine atoms at C_2 and C_5 of both dianhydrides through their interaction with phosphorus tribromide. This also failed, but an interesting and unexpected effect of this reagent on these compounds was observed. When 1 : 4-3 : 6-dianhydromannitol was treated with phosphorus tribromide in carbon tetrachloride first at −10° and then at 50°, no 2 : 5-dibromo-derivative could be isolated; instead, ring scission occurred and the main product was a crystalline dibromo hexitol, which gave rise to a tetra-acetyl derivative. Proof of the structure of this dibromo hexitol was obtained by its conversion into a dimethylene derivative, which on treatment with sodium iodide and acetone readily exchanged its two bromine atoms for iodine, thus giving a compound identical with the 1 : 6-di-iodo 2 : 4-3 : 5-dimethylene mannitol of Micheel (*Annalen*, 1932, **496**, 77). Therefore the dibromo dimethylene hexitol from which this was obtained must be 1 : 6-*dibromo* 2 : 4-3 : 5-*dimethylene mannitol* (V), and the original dibromo hexitol, 1 : 6-*dibromo mannitol* (IV), the acetyl derivative of which must be 1 : 6-*dibromo* 2 : 3 : 4 : 5-*tetra-acetyl mannitol*.

Ring scission of 1 : 4-3 : 6-dianhydromannitol must have taken place with addition of bromine atoms at C_1 and C_6. Such ring scission, however, did not occur on treatment of the


(IV.)


(V.)


(VI.)

dianhydride with hydrobromic acid, either at room temperature or at 50°, so that it is probable that the phosphorus tribromide itself, and not the hydrogen bromide formed by its hydrolysis, is responsible for the ring scission.

Similar treatment of 1 : 4-3 : 6-dianhydrosorbitol with phosphorus tribromide gave a dibromo hexitol isolated as its dibenzylidene derivative, which by analogy with the corresponding mannitol derivative must be 1 : 6-*dibromo* 2 : 4-3 : 5-*dibenzylidene sorbitol*. This on treatment with sodium iodide in acetone at 100° gave a little over 50% yield of sodium bromide, indicating that both bromine atoms were attached to primary carbon atoms. The product isolated from this reaction, however, was a monobromo monoiodo dibenzylidene sorbitol. This preferential reaction at one end of the sorbitol molecule has been observed many times by us, and an account of it has been published by Ness, Hann, and Hudson (*J. Amer. Chem. Soc.*, **1944**, **66**, 1901) who found, for example, that treatment of 1 : 6-ditosyl dimethylene sorbitol with sodium iodide gave mainly 6-iodo 1-tosyl dimethylene sorbitol. By analogy, therefore, the product obtained now is probably 1-*bromo* 6-*iodo* 2 : 4-3 : 5-*dibenzylidene sorbitol* (it is practically certain that the benzylidene groups are in this position since in all other similar compounds previously examined this has been found to be so). The same 1 : 6-dibromo dibenzylidene sorbitol was isolated after 1 : 4-3 : 6-dianhydrosorbitol had been treated at 100—110° with 50% hydrobromic acid, though some monobromo monobenzylidene monoanhydrosorbitol (A) was also isolated. It has been shown already that, under similar conditions when hydrochloric acid was the hydrolytic agent, the 3 : 6-anhydro-ring in 1 : 4-3 : 6-dianhydrosorbitol was more easily broken than the 1 : 4 ring. In this way 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol was obtained and its structure proved by Montgomery and Wiggins in Part IX of this series (this vol., p. 237). Therefore the hydrobromic acid reaction product (A) is most probably 6-*bromo* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* (VI).

Experimental.

2 : 5-*Dichloro* 1 : 4-3 : 6-*Dianhydrosorbitol*.—An attempt to prepare this, following precisely the method successful in the case of the mannitol analogue (Wiggins, *loc. cit.*), failed. The following procedure did give a small amount of the compound. 1 : 4-3 : 6-Dianhydrosorbitol (1 g.) was suspended in benzene containing thionyl chloride, and the mixture boiled for 6 hours. Thereafter the solvent was evaporated and the syrupy residue heated with phosphorus pentachloride for 1 hour at 140°. The product was dissolved in chloroform and washed with dilute sodium carbonate solution and then with water, and the chloroform solution dried ($MgSO_4$) and evaporated to a thin syrup. This was then distilled, but there was extensive decomposition, and only a small amount (0·15 g.) of 2 : 5-*dichloro* 1 : 4-3 : 6-*dianhydrosorbitol*, b. p. 105°/15 mm. (74°/0·01 mm.), was obtained; $[\alpha]_D^{19°}$ +55·8° in chloroform (*c*, 4·015), $n_D^{17°}$ 1·5269 (Found : Cl, 38·3. $C_6H_8O_2Cl_2$ requires Cl, 38·8%).

Monochloro 1 : 4-3 : 6-*Dianhydrosorbitol*.—Finely powdered 1 : 4-3 : 6-dianhydrosorbitol (5 g.) was heated in dry xylene (50 c.c.) with thionyl chloride (10 c.c.) until solution was complete. The solution was then evaporated to a syrup which was dissolved in dry pyridine (10 c.c.), thionyl chloride (10 c.c.) added, and the mixture heated at 120—140° for 4 hours. The dark liquid was poured into ice–water, and the solution left overnight and then extracted with chloroform. The extract was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, and was then dried ($MgSO_4$) and evaporated to a syrup which distilled at 200—220° (bath temp.)/12 mm. The distillate (1·7 g.) partly crystallised, and was recrystallised from ether, to form long needles, m. p. 63—64°, $[\alpha]_D^{19°}$ +48·0° in chloroform (*c*, 1·625). It is suggested that this compound is 5-*chloro* 1 : 4-3 : 6-*dianhydrosorbitol* (Found : C, 43·6; H, 5·5; Cl, 20·0. $C_6H_9O_3Cl$ requires C, 43·8; H, 5·5; Cl, 21·6%).

Action of Phosphorus Tribromide on 1 : 4-3 : 6-*Dianhydromannitol*.—The dianhydride (14·7 g.) was finely powdered and stirred into carbon tetrachloride (200 c.c.). The suspension was cooled to −10°, and phosphorus tribromide (51·5 g., 2 mols.) added with stirring during 10 hours. The mixture was then heated at 50° for 3 hours. A brown syrup appeared on the surface of the carbon tetrachloride which was removed by distillation. To the residue, ice was added, and after the resulting solution had been kept overnight a solid separated. This was collected and recrystallised from water to form white plates of 1 : 6-*dibromo mannitol*, m. p. 177—178° (decomp.), $[\alpha]_D^{18°}$ −2·6° in water (*c*, 0·765) (Found : C, 22·7; H, 3·8; Br, 51·8. $C_6H_{12}O_4Br_2$ requires C, 23·3; H, 3·9; Br, 51·9%).

1 : 6-*Dibromo* 2 : 3 : 4 : 5-*Tetra-acetyl Mannitol*.—1 : 6-Dibromo mannitol (0·3 g.), fused sodium

acetate (0·2 g.), and acetic anhydride (5 c.c.) were refluxed for 15 minutes. The solution was poured into water, and the solid, which rapidly separated, filtered off. Recrystallised from alcohol–water, the *tetra-acetyl* derivative had m. p. 125—126° (Found: C, 35·0; H, 4·0. $C_{14}H_{20}O_8Br_2$ requires C, 35·3; H, 4·2%).

1 : 6-*Dibromo* 2 : 4-3 : 5-*Dimethylene Mannitol.*—The compound (1 g.) was finely powdered and suspended in 40% formaldehyde solution (10 c.c.), and the mixture saturated with hydrogen chloride at 0°. The crystalline material dissolved, and an oily product separated which partly crystallised on long refrigeration. The crystals were separated and freed from occluded syrup by pressing them on a porous tile. After being recrystallised from methyl alcohol–chloroform, these had m. p. 178—179°, $[\alpha]_D^{18°}$ +72·4° in chloroform (*c*, 5·52), and were 1 : 6-*dibromo* 2 : 4-3 : 5-*dimethylene mannitol* (Found: C, 28·8; H, 3·8. $C_8H_{12}O_4Br_2$ requires C, 28·4; H, 3·9%).

Conversion of 1 : 6-*Dibromo* 2 : 4-3 : 5-*Dimethylene Mannitol into* 1 : 6-*Di-iodo* 2 : 4-3 : 5-*Dimethylene Mannitol.*—1 : 6-Dibromo dimethylene mannitol (0·24 g.) was heated at 105° for 5 hours in a sealed tube with acetone (10 c.c.) and sodium iodide (0·33 g.; 3 mols.), using anhydrous reagents. Sodium bromide separated. The liquid was then evaporated to dryness and the residue extracted with chloroform–water mixture. The chloroform layer was separated and washed with dilute sodium thiosulphate and with water, and then dried ($MgSO_4$). On evaporation of the solvent a crystalline residue was obtained which, recrystallised from alcohol, had m. p. 195—196° alone or in admixture with authentic 1 : 6-di-iodo 2 : 4-3 : 5-dimethylene mannitol; $[\alpha]_D$ +50·0° in chloroform (*c*, 0·499). Micheel (*loc. cit.*) gives m. p. 195°, $[\alpha]_D$ +50·2°.

Action of Hydrobromic Acid on 1 : 4-3 : 6-*Dianhydromannitol.*—(a) *At room temperature.* The dianhydride (3·3 g.) was treated with 10% hydrobromic acid (25 c.c.) for 24 hours at room temperature. Thereafter the acid was neutralised with silver carbonate, the solution filtered, and the filtrate evaporated to dryness. The residue was extracted with ethyl acetate and the extract evaporated to a syrup which crystallised on nucleation with 1 : 4-3 : 6-dianhydromannitol. It was recrystallised from ethyl acetate; yield 3·1 g., m. p. 86—87° alone or in admixture with an authentic specimen.

(b) *At* 50°. From the dianhydride (3·4 g.), treated with 10% hydrobromic acid (25 c.c.) at 50° for 3 hours then overnight at room temperature and worked up as above, 3·0 g. of the dianhydride were recovered unchanged.

Action of Phosphorus Tribromide on 1 : 4-3 : 6-*Dianhydrosorbitol.*—Finely powdered dianhydrosorbitol (10 g.) was suspended in dry carbon tetrachloride (150 c.c.), and phosphorus tribromide (13 c.c., 2 mols.) added with stirring during ½ hour. The stirring was continued for a further 2 hours at 50—70°. The resulting mixture was cooled, and the carbon tetrachloride decanted from the syrupy product, which was extracted with ethyl acetate. This extract gave a syrup (6 g.) which contained phosphorus tribromide and other products which rapidly decomposed, so that no information could be obtained concerning them. The material insoluble in ethyl acetate (1·8 g.) was shaken with benzaldehyde (10 c.c.) and zinc chloride (2 g.) for 24 hours. The product was evaporated with an aqueous solution of sodium carbonate (2 g.) until all the benzaldehyde had been removed. The solution was then evaporated to dryness, and the residue extracted with chloroform. This gave, on evaporation, a syrup (1·7 g.) which crystallised. Recrystallised from alcohol it gave 1 : 6-dibromo dibenzylidene sorbitol, m. p. 226—227° alone or in admixture with the material obtained below, and showed $[\alpha]_D^{18°}$ +15·1° in chloroform (*c*, 1·325).

Action of Hydrobromic Acid on 1 : 4-3 : 6-*Dianhydrosorbitol.*—The dianhydride (30 g.) was heated in sealed tubes with 50% hydrobromic acid (150 c.c.) for 30 hours at 100—110°. The dark brown liquid was filtered with charcoal and evaporated under reduced pressure until as much as possible of the hydrobromic acid had been removed. The residual syrup was shaken with benzaldehyde (150 c.c.) containing anhydrous zinc chloride (30 g.) for 48 hours. The resulting solution was distilled under reduced pressure with an aqueous solution of sodium carbonate (60 g.) until no more benzaldehyde distilled. Thereafter it was evaporated to a syrup which deposited a few crystals of 1 : 6-*dibromo dibenzylidene sorbitol*; these, separated and recrystallised from alcohol–water, had m. p. 226—227°, $[\alpha]_D^{18°}$ +15·3° in chloroform (*c*, 1·32) (Found: C, 50·2; H, 4·5; Br, 32·1. $C_{20}H_{20}O_4Br_2$ requires C, 50·0; H, 4·2; Br, 33·1%). The alcoholic mother liquors were evaporated to a syrup, which was extracted with water. This extract deposited crystals (0·1 g.) of a monobromo monobenzylidene monoanhydrosorbitol, probably 6-*bromo* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* which, after being recrystallised from alcohol, had m. p. 136—138°, $[\alpha]_D^{24°}$ +16·5° in chloroform (*c*, 1·09) (Found: C, 49·5; H, 5·0. $C_{13}H_{15}O_4Br$ requires C, 49·5; H, 4·8%). From the aqueous mother liquors, unchanged dianhydrosorbitol (8·1 g.) was recovered.

1-*Bromo* 6-*Iodo* 2 : 4-3 : 5-*Dibenzylidene Sorbitol.*—1 : 6-Dibromo 2 : 4-3 : 5-dibenzylidene sorbitol (0·09 g.) was dried and heated at 100—110° for 6 hours in a sealed tube with dry sodium iodide (0·1 g.) in dry acetone (10 c.c.). Crystals of sodium bromide separated [0·02 g., 52% (assuming 2 mols.)]. The acetone solution was evaporated to dryness, and the residue extracted with chloroform. The extract was washed with sodium thiosulphate solution and with water, dried ($MgSO_4$), filtered, and evaporated. The residual 1-*bromo* 6-*iodo* 2 : 4-3 : 5-*dibenzylidene sorbitol*, recrystallised from alcohol–acetone, had m. p. 232—233° $[\alpha]_D^{23°}$ +25·4° in chloroform (*c*, 1·71) (Found: C, 44·9; H, 3·9. $C_{20}H_{20}O_4BrI$ requires 45·2; H, 3·8%).

The authors thank Professor Sir Norman Haworth, F.R.S., and Dr. J. L. Simonsen, F.R.S., for their interest, and the Colonial Products Research Council for financial aid.

THE A. E. HILLS LABORATORIES,
THE UNIVERISTY, EDGBASTON, BIRMINGHAM, 15. [*Received, February 16th*, 1948.]

448. *Anhydrides of Polyhydric Alcohols. Part XII. The Reaction between Mannitol and Hydrochloric Acid.*

By R. Montgomery and L. F. Wiggins.

The reaction between mannitol and hydrochloric acid has been studied in detail. Either 1 : 6-dichloro mannitol or 1 : 4-3 : 6-dianhydromannitol can be obtained as the main product according to the experimental conditions. In addition, numerous other anhydrides of mannitol or their derivatives have been isolated. The presence of 1 : 5-anhydromannitol (styracitol), 1 : 4-anhydromannitol (mannitan), and 1 : 5-3 : 6-dianhydromannitol (neomannide) has been detected. A new hexitol dianhydride of unknown constitution has been isolated as such and as its bismethanesulphonate, and yet another dianhydride as its bismethanesulphonate only. A derivative of monochloro monoanhydromannitol, probably 6-chloro 1 : 4-anhydromannitol, and a dichloro-derivative of monoanhydromannitol, probably either 2 : 6- or 1 : 2-dichloro 1 : 4-anhydromannitol, were encountered.

When mannitol is treated with boiling concentrated hydrochloric acid for a long period, 1 : 4-3 : 6-dianhydromannitol is formed in yields about 35% (Wiggins, *J.*, 1945, 4; Montgomery and Wiggins, *J.*, 1947, 433). On the other hand, mannitol heated with fuming hydrochloric acid under pressure affords 1 : 6-dichloro mannitol in yields of about 40% (Haworth, Heath, and Wiggins, *J.*, 1944, 155). It is of interest to discover what other products are formed in each of these reactions and to discover the relationship between them. Some effort toward this end has now been made, and although the position has been found to be very complicated, and a complete picture of the reactions going on has not yet been acquired, the results so far obtained are of sufficient interest to warrant publication.

A solution of mannitol in concentrated hydrochloric acid was boiled for 72 hours, and the syrup so obtained separated by distillation into four fractions, the first two of which crystallised and after recrystallisation yielded 1 : 4-3 : 6-dianhydromannitol in 27% yield. The last two fractions were combined with the residues from the crystallisation and fractionally distilled into seven parts. The methanesulphonyl derivatives of each of these fractions were prepared. The first three fractions gave 2 : 5-*bismethanesulphonyl* 1 : 4-3 : 6-*dianhydromannitol*, m. p. 104°, identical with authentic material. These fractions also contained 2-*chloro* 5-*methanesulphonyl* 1 : 4-3 : 6-*dianhydromannitol* (5-chloro 2-methanesulphonyl 1 : 4-3 : 6-dianhydromannitol) (see below), thus showing the presence of 2(5)-chloro 1 : 4-3 : 6-dianhydromannitol (I). In the higher-boiling fractions, three new *dianhydrohexitols* were isolated. One (A) was isolated as such (m. p. 118—119°, $[\alpha]_D$ — 33·6°) and as its *bismethanesulphonate*, m. p. 139—140°. The other two, (B) and C), were isolated as their bismethanesulphonates only (m. p. 190—191° and 113—114° respectively). A convenient way of isolating dianhydrohexitol (A) was by benzylidenation of the accompanying materials in the fraction in which it occurred, and it was then possible to isolate it by distillation since it formed no benzylidene derivative. Treatment of the highest-boiling fraction with benzaldehyde gave a crystalline *chloro benzylidene anhydrohexitol*, m. p. 172°. Mannitan (1 : 4-anhydromannitol), although not isolated here, was produced by brief treatment of mannitol with hydrochloric acid (Wiggins, *loc. cit.*).

Thus it is seen that this reaction produces a monoanhydromannitol, a derivative of a monoanhydrohexitol which may also be a mannitol derivative; and no fewer than four different dianhydrides. Since the conditions under which these substances have been formed preclude the existence of the less stable three- or four-membered rings (no examples of the latter have ever been described in the hexitol series), only hydrofuranol or hydropyranol ring systems need be considered. This being the case, there are only three such dianhydrides of mannitol which are sterically possible, namely 1 : 4-3 : 6-, 1 : 5-3 : 6-, and 1 : 5-2 : 6-. Since we have obtained four dianhydrides, Walden inversion must have occurred in the formation of one or more of them, so that they cannot all be of the mannitol configuration. Of the three possible dianhydrides of mannitol, two have been described previously, namely "*iso*mannide" (1 : 4-3 : 6-dianhydromannitol) and "neomannide" (1 : 5-3 : 6-dianhydromannitol) (II*a*, II*b*), the latter having been synthesized and its structure proved by Hockett and Sheffield (*J. Amer. Chem. Soc.*, 1946, **68**, 937). A third dianhydromannitol called "β-mannide" was obtained by Siwoloboff (*Annalen*, 1886, **233**, 372) and had m. p. 119°, $[\alpha]_D$ + 94°, but the constitution of this has not yet been determined; by a process of elimination, however, it should be 1 : 5-2 : 6-dianhydromannitol, though no other workers have yet obtained this substance. The properties of these anhydrides of mannitol are summarised in the Table.

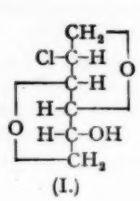
The dianhydrohexitol (A) showed m. p. 118°. This is very close to that described by Siwoloboff for β-mannide, though the specific rotation was $[\alpha]_D$ — 33·6°, a value quite different

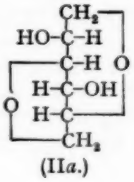
Properties of mannitol anhydrides.

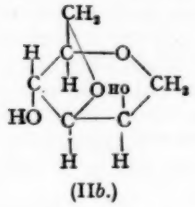
Anhydride.	M. p.	$[\alpha]_D$.	Reference.
" *iso*Mannide " (1 : 4-3 : 6-dianhydromannitol)	86—87°	+91·0°	Wiggins (*J.*, 1945, 4).
" Neomannide " (1 : 5-3 : 6-dianhydromannitol)	112·8—113·3	+ 6·4	Hockett and Sheffield (*loc. cit.*).
" β-Mannide "	119	+94·05	Siwoloboff (*loc. cit.*).
" Mannitan " (1 : 4-anhydromannitol)	145—147	−23·75	Valentin (*Coll. Czech. Chem. Comm.*, 1936, **8**, 35).
" Styracitol " (1 : 5-anhydromannitol)	145—155	−50·9	Hockett and Conley (*J. Amer. Chem. Soc.*, 1944, **66**, 464).

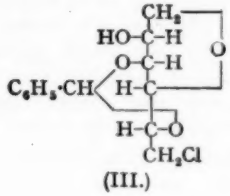
from that of β-mannide, so that the two cannot be identical. Dianhydrohexitols (B) and (C) were isolated here only as the bismethanesulphonates. The bismethanesulphonate of 1 : 5-3 : 6-dianhydromannitol (neomannide) has now been prepared and found to be identical in respect to m. p., specific rotation, and mixed m. p. with the bismethansulphonate of dianhydride (B). No clue as to the identity of the dianhydride (C) has been obtained.

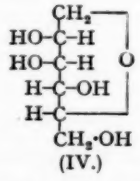
Of the monoanhydro-derivatives isolated from the reaction in question, mannitan is readily detected and recognised when the time of heating is approximately 12 hours. The other monoanhydride isolated was a monochloro monobenzylidene derivative. This compound is probably 6-chloro 3 : 5-benzylidene 1 : 4-anhydromannitol (III) which could very well be produced by the partial ring-opening of the main product of the reaction, namely 1 : 4-3 : 6-dianhydromannitol, followed by its benzylidenation. This, however, is a tentative suggestion.

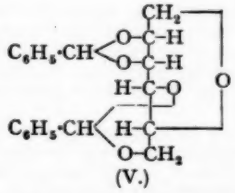

(I.)

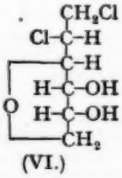

(II*a*.)

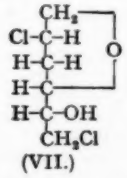

(II*b*.)


(III.)


(IV.)


(V.)


(VI.)


(VII.)

When mannitol is treated with fuming hydrochloric acid under pressure, the main product is 1 : 6-dichloro mannitol, isolated in about 40% yield (Haworth, Heath, and Wiggins, *J.*, 1944, 155). Now it has been found that 1 : 4-3 : 6-dianhydromannitol is formed as well in this reaction, because it has been isolated as such from the by-products as its bismethanesulphonate and as 2-chloro 1 : 4-3 : 6-dianhydromannitol. The latter was identified as its 5-methanesulphonate and by the fact that it was transformed by phosphorus pentachloride into 2 : 5-dichloro 1 : 4-3 : 6-dianhydromannitol identical with an authentic specimen. These products were isolated by fractional distillation of the residue from the crystallisation of the 1 : 6-dichloro mannitol, and were encountered in the lower-boiling fraction. From a higher-boiling fraction after benzylidenation, a chloro benzylidene anhydrohexitol, m. p. 172—173°, was isolated. This was identical with the compound encountered among the products of the action of boiling hydrochloric acid on mannitol. In addition, a new dibenzylidene hexitol, m. p. 192°, was obtained, identical with the dibenzylidene derivative of styracitol, here described for the first time. The styracitol (IV) was prepared from tetra-acetyl oxyglucal by the method of Hockett and Conley (*loc. cit.*). This on benzylidenation gave *dibenzylidene styracitol* identical with the dibenzylidene hexitol, m. p. 192°. Its structure will most probably be represented by (V) because dibenzylidene mannopyranose has been shown to have this orientation of its benzylidene residues. Another monoanhydrohexitol derivative was isolated from the high-boiling fraction, namely a *dichloro anhydrohexitol.* Since it has been definitely shown that 2-chloro 1 : 4-3 : 6-dianhydromannitol was present, the dichloro anhydrohexitol may well have arisen through the partial ring scission of this derivative of the dianhydride. If the

1 : 4-ring opened, then 1 : 2-dichloro 3 : 6-anhydromannitol (VI) would result, whereas if the 3 : 6-ring suffered scission, then 2 : 6-dichloro 1 : 4-anhydromannitol (VII) would be formed, and future work must decide this issue. Owing to the symmetry of the mannitol molecule, (VI) and (VII) are identical with 5 : 6-dichloro 1 : 4-anhydromannitol and 1 : 5-dichloro 3 : 6-anhydromannitol respectively.

From these results the way in which these products occur may be suggested. Boiling hydrochloric acid effects the dehydration of mannitol as do other acid catalysts. This may involve, however, the preliminary attachment of the anion, in this case a chloro-group, to the primary carbon atoms. The main dehydration product, nevertheless, is the dihydrofuranol ring system—1 : 4-3 : 6-dianhydromannitol—which is formed in stages: first the 1 : 4-ring, then the dianhydride. This is so because 1 : 4-anhydromannitol (mannitan) is isolated when the reaction is allowed to proceed for a short time only. This dehydration is accompanied by the formation of smaller amounts of other types of ring products, namely the 1 : 5-ring in styracitol and the 1 : 5-3 : 6-rings in neomannide. The treatment with hydrochloric acid also effects partial replacement of the secondary hydroxyl groups shown by the isolation of 2-chloro 1 : 4-3 : 6-dianhydromannitol under both sets of conditions, although much more is found amongst the products of the more drastic reaction. Since much more 1 : 6-dichloro mannitol than 1 : 4-3 : 6-dianhydromannitol is isolated under these more drastic conditions, we may envisage the main reaction as being an equilibrium between the following reactants:

$$\text{1 : 4-3 : 6-Dianhydromannitol} + HCl \rightleftharpoons \text{1 : 6-dichloro mannitol} + H_2O.$$

Thus the reaction of mannitol with excess of hydrochloric acid under pressure will favour the production of 1 : 6-dichloro mannitol, whilst the reaction under reflux, in which much less hydrochloric acid is present, favours the formation of the 1 : 4-3 : 6-dianhydride. The total yield of 1 : 6-dichloro mannitol obtained after numerous re-treatments of the residues from the reaction of mannitol with fuming hydrochloric acid under pressure is limited to about 40% (Haworth, Heath, and Wiggins, *loc. cit.*). This is doubtless due to substitution of the secondary hydroxyl groups in 1 : 4-3 : 6-dianhydromannitol or in 1 : 6-dichloro mannitol, and also to the formation of ring systems which are still more difficult to open than the hydrofuranol type.

Experimental.

Action of Concentrated Hydrochloric Acid on Mannitol.—(*a*) Mannitol (900 g.) was boiled under reflux with concentrated hydrochloric acid (5 l.) for 3½ days, and the resulting dark liquid evaporated to a syrup. This was dissolved in water, and the solvent again evaporated to remove most of the hydrochloric acid. The residual liquid was distilled into the following fractions: I, 219·8 g., b. p. 135—145°/11 mm.; II, 27·0 g., b. p. 150—157°/11 mm.; III, 95·0 g., b. p. 160—190°/10 mm.; IV, 62·0 g., b. p. 160—190°/0·01 mm.

Fraction I crystallised, and on recrystallisation from ethyl acetate yielded 1 : 4-3 : 6-dianhydromannitol (155·8 g.), m. p. 85—87°. Fraction II similarly gave 8 g. of dianhydromannitol. The mother liquors were evaporated and the residue refractionated, and a further 28·3 g. of dianhydromannitol separated. The mother liquors were again evaporated and the residues combined with fractions III and IV, and the whole carefully refractionated together. The final fractions collected were: (1), 7·3 g., b. p. 135—145°/13 mm., $n_D^{18°}$ 1·5011; (2), 21·9 g., b. p. 145—150°/12 mm., $n_D^{18°}$ 1·5041; (3), 15·0 g., b. p. 150—168°/11 mm., $n_D^{18°}$ 1·5042; (4), 20·3 g., b. p. 165—173°/12 mm., $n_D^{18°}$ 1·5071; (5), 22·8 g., b. p. 177—185°/10 mm., $n_D^{18°}$ 1·5092; (6), 43·7 g., b. p. 190—196/10 mm., $n_D^{18°}$ 1·5130; (7), 13·3 g., b. p. 196—210°/10 mm., residue, 40·0 g.

Fractions (1—5) did not crystallise and were each dissolved (1 g.) in dry pyridine (15 c.c.) and treated with methanesulphonyl chloride (2 c.c.) at 0°. After being kept for 3 days at room temperature the mixture was poured into ice–water and the product extracted with chloroform. The combined extracts were washed successively with 5N-sulphuric acid, sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$). The solvent was evaporated, and the residue fractionally recrystallised from alcohol–acetone. The following compounds were obtained from each fraction.

Fraction 1. (*a*) 2 : 5-Bismethanesulphonyl 1 : 4-3 : 6-dianhydromannitol, m. p. 101—102°; (*b*) 2-chloro 5-methanesulphonyl 1 : 4-3 : 6-dianhydromannitol, m. p. 114—115°, $[\alpha]_D^{23°}$ + 64·4° in chloroform (*c*, 1·645).

Fraction 2. (*a*) 2 : 5-Bismethanesulphonyl 1 : 4-3 : 6-dianhydromannitol, m. p. 101—102°; (*b*) 2-chloro 5-methanesulphonyl 1 : 4-3 : 6-dianhydromannitol, m. p. 114—115°.

Fraction 3. 2 : 5-Bismethanesulphonyl 1 : 4-3 : 6-dianhydromannitol, m. p. 101—102°.

Fraction 4. (*a*) 2 : 5-Bismethanesulphonyl 1 : 4-3 : 6-dianhydromannitol, m. p. 101—102; (*b*) *bismethanesulphonyl dianhydrohexitol* (*A*), m. p. 140—141°, $[\alpha]_D^{21°}$ −28·9° in chloroform (*c*, 1·38) (Found: C, 32·2; H, 4·3. $C_8H_{14}O_8S_2$ requires C, 31·8; H, 4·6%).

Fraction 5. (*a*) 2 : 5-Bismethanesulphonyl 1 : 4-3 : 6-dianhydromannitol, m. p. 101°; (*b*) bismethanesulphonyl dianhydrohexitol (A), m. p. 139—140°; (*c*) *bismethanesulphonyl dianhydrohexitol* (B), m. p. 190—191°, $[\alpha]_D$ + 14° in acetone (*c*, 0·85) (Found: C, 32·0; H, 4·9; S, 21·9. $C_8H_{14}O_8S_2$ requires C, 31·8; H, 4·6; S, 21·2%). An attempt to prepare a benzylidene derivative from this fraction resulted in recovery of the starting material in good yield.

Fraction 6. This partly crystallised. The crystals were drained from syrup. The *dianhydro-*

hexitol (A), after recrystallisation from ethyl acetate, had m. p. 118—119°, $[\alpha]_D$ − 33·6° in water (*c*, 1·25) (Found: C, 49·7; H, 7·2. $C_6H_{14}O_4$ requires C, 49·5; H, 6·9%). Treatment of fraction 6 with methanesulphonyl chloride gave (*a*) bismethanesulphonyl dianhydrohexitol (A), m. p. 139—140°, (*b*) bismethanesulphonyl dianhydrohexitol (B), m. p. 190—191°, (*c*) a *bismethanesulphonate* of the dianhydrohexitol (C), m. p. 113—114°, $[\alpha]_D^{19°}$ − 22·6° in chloroform (*c*, 1·855) (Found: C, 31·9; H, 4·1; S, 20·8%).

Benzylidenation of fraction 6. The syrup (3 g.) was shaken with benzaldehyde (50 c.c.) and zinc chloride (4 g.) for 24 hours. The solution was then treated with excess of aqueous sodium carbonate and the excess of benzaldehyde removed by steam distillation. The residue, obtained by evaporation of the solution to dryness, was extracted 4 times with 100-c.c. portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated to dryness. The residue (2·1 g.) distilled at 220—230° (bath temp.)/12 mm. as a colourless oil (0·5 g.) which crystallised completely, and on recrystallisation from ethyl acetate had m. p. 118—119° and was identical with the dianhydrohexitol (A). Benzylidenation has therefore purified this from other material which has undergone condensation with benzaldehyde.

Fraction 7. This was partly crystalline. The crystals were the dianhydrohexitol (A), m. p. 118—119°. Treatment of this fraction 7 with methanesulphonyl chloride gave (*a*) bismethanesulphonyl dianhydrohexitol (A), m. p. 139—140°, (*b*) bismethanesulphonyl dianhydrohexitol (B), m. p. 191—192°.

Benzylidenation of fraction 7. The syrup (3·35 g.) was shaken with benzaldehyde (50 c.c.) and zinc chloride (4 g.) and the product isolated as described previously. It partly crystallised, and after recrystallisation from alcohol a compound with the composition of a chloro benzylidene anhydrohexitol was isolated, m. p. 172—173°.

Action of Fuming Hydrochloric Acid on Mannitol.—Mannitol (75 g.) was heated in sealed tubes at 100° for 36 hours with fuming hydrochloric acid (600 c.c.) as described by Haworth, Heath, and Wiggins (*loc. cit.*). The resulting brown liquid was evaporated under reduced pressure to a semi-solid mass which was dissolved in water, filtered with charcoal, and again evaporated. The product was taken up in a little water and allowed to cool; crystals of 1 : 6-dichloro mannitol, m. p. 174°, then separated (18 g.). The mother liquors were evaporated and the residue distilled under reduced pressure. The following fractions were collected: A, 20 g., b. p. 150—180° (bath temp.)/25 mm.; B, 9·7 g., b. p. 200—220° (bath temp.)/0·1 mm. A small fraction between A and B was not examined further.

Fraction A. This partly crystallised, and the crystals were separated on a tile. They were 1 : 4-3 : 6-dianhydromannitol (1 g.), m. p. 86—87° alone or in admixture with an authentic specimen. The tile was extracted with boiling water and the extract evaporated to a syrup which was distilled and collected in two portions: (*a*) b. p. 115—120° (bath temp.)/0·04 mm., $n_D^{18°}$ 1·5030 (Found: C, 44·8; H, 5·8; Cl, 16·8%); (*b*) b. p. 120—125° (bath temp.)/0·02 mm., $n_D^{18°}$ 1·5035 (Found: C, 44·7; H, 5·8; Cl, 16·2. Calc. for $C_6H_9O_3Cl$: C, 43·8; H, 5·4; Cl, 21·5%).

Both (*a*) and (*b*) were essentially monochloro dianhydromannitol. Fraction (*a*) was heated with phosphorus pentachloride at 130° for 1 hour, and the resulting mixture diluted with chloroform and washed successively with dilute sodium hydrogen carbonate solution and water. The extract, after being dried ($MgSO_4$), was evaporated and the product distilled at 90° (bath temp.)/0·07 mm. The distillate crystallised and was recrystallised from ether–petrol; m. p. 62—64° alone or in admixture with 2 : 5-dichloro 1 : 4-3 : 6-dianhydromannitol.

Fraction (*a*) was also treated with methanesulphonyl chloride, and the product found to contain 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydromannitol, m. p. 102—103°, and *2-chloro 5-methanesulphonyl* 1 : 4-3 : 6-*dianhydromannitol*, m. p. 115—117°, $[\alpha]_D^{23}$ + 66·4° in chloroform (*c*, 1·645) (Found: Cl, 15·2. $C_7H_{11}O_5ClS$ requires Cl, 14·8%).

Fraction B. This partly crystallised. The crystals of a *dichloro anhydrohexitol* were separated and recrystallised from ethyl acetate, and had m. p. 216—217°, $[\alpha]_D^{22°}$ + 27·8° in alcohol (*c*, 1·295) (Found: C, 35·8; H, 5·1; Cl, 35·4. $C_6H_{10}O_3Cl_2$ requires C, 35·8; H, 5·0; Cl, 35·5%). Benzylidenation of fraction B (9 g.) with benzaldehyde (50 c.c.) and anhydrous zinc chloride (10 g.), the mixture being poured, after 24 hours' shaking, into petrol–water, gave a syrup which partly crystallised and on fractional recrystallisation yielded (1) *dibenzylidene styracitol* (see below), m. p. 192° undepressed by admixture with an authentic specimen (Found: C, 70·8; H, 6·0. $C_{20}H_{20}O_5$ requires C, 70·6; H, 6·0%). (2) A *chloro benzylidene anhydrohexitol*, m. p. 171—172° (Found: C, 57·1; H, 5·3. $C_{13}H_{15}O_4Cl$ requires C, 57·7; H, 5·5%).

Neomannide (1 : 5-3 : 6-*Dianhydromannitol*).—This was synthesised according to the procedure outlined by Hockett and Sheffield (*loc. cit.*).

Bismethanesulphonyl Neomannide.—Neomannide (50 mg.) was dissolved in dry pyridine (3 c.c.), and methanesulphonyl chloride (0·2 c.c.) added at 0°. The mixture was kept overnight, then poured into ice–water. The crystalline precipitate was collected, washed with water, and recrystallised from alcohol–acetone, forming small needles, m. p. 188—189° alone or in admixture with the bismethanesulphonyl dianhydrohexitol (B) obtained above; $[\alpha]_D$ + 11·1 in acetone (*c*, 0·90). The *bismethanesulphonyl dianhydrohexitol*, m. p. 190°, had $[\alpha]_D$ + 11·5 in acetone (*c*, 0·965) (Found: C, 32·3; H, 4·9. $C_8H_{14}O_8S_2$ requires C, 31·8; H, 4·6%).

Styracitol (1 : 5-*anhydromannitol*).—This was obtained by the hydrogenation of tetra-acetyl oxyglucal according to the procedure of Hockett and Conley (*loc. cit.*).

Dibenzylidene styracitol. Styracitol (0·3 g.) and zinc chloride (0·2 g.) were shaken with benzaldehyde (5 c.c.) for 24 hours. Sodium carbonate (0·5 g.) in water was added and the excess of benzaldehyde removed by steam distillation under reduced pressure. The solution was evaporated to dryness and the residue extracted with chloroform. The chloroform extract was evaporated, and a crystalline residue obtained. This, recrystallised from alcohol, formed feathery needles, m. p. 192°.

2 : 3 : 4 : 6-*Tetrakismethanesulphonyl styracitol.* Styracitol (0·1 g.) was dissolved in dry pyridine and methanesulphonyl chloride (0·5 g.) at 0°. The mixture was kept for 24 hours and then poured into ice–water. The precipitated *tetrakismethanesulphonate* was collected, washed with water, dried, and recrystallised from acetone containing a little ligroin. It formed small needles, m. p. 171—172° Found: C, 25·5; H, 4·3. $C_{10}H_{20}O_{13}S_4$ requires C, 26·0; H, 4·2%).

2 : 5-*Bismethanesulphonyl* 1 : 4-3 : 6-*dianhydromannitol*.—Dianhydromannitol (20 g.) was dissolved in dry pyridine (100 c.c.), and methanesulphonyl chloride (30 c.c., 2·1 mols.) carefully added at 0°. The mixture was kept for several days at room temperature and then poured into ice–water. The precipitated **2 : 5-*bismethanesulphonate*** was collected and washed with water; recrystallised from alcohol–acetone, it formed colourless plates (28 g.), m. p. 104°, $[\alpha]_D^{18°}$ + 138·7° in chloroform (*c*, 1·775) (Found: C, 32·2; H, 4·6. $C_8H_{14}O_8S_2$ requires C, 31·8; H, 4·6%).

The authors are grateful to Professor Sir Norman Haworth, F.R.S., for his interest, and to the Colonial Products Research Council for financial support.

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15. [*Received, February 16th*, 1948.]

---

449. *Compounds of Diarylcyanoarsine Type.*

By L. J. GOLDSWORTHY, W. H. HOOK, J. A. JOHN, S. G. P. PLANT, J. RUSHTON, and L. M. SMITH.

A considerable number of diarylarsonous acids have been made by the use of the Bart reaction, and converted by reduction in the presence of hydrochloric acid into the corresponding diarylchloroarsines. From these and other diarylchloroarsines obtained by alternative methods many diarylcyanoarsines have been prepared.

DURING investigations undertaken in order to obtain a series of compounds of diarylcyanoarsine type, AsRR'·CN, the reaction of Bart (D.R.-P. 250,264; *Chem. Zentr.*, 1912, ii, 882; *Annalen*, 1922, **429**, 55) has been applied to the preparation of a number of diarylarsonous acids, AsRR'O·OH.* It is of interest that although phenyl- and the three tolyl-arsenious oxides, R·AsO, readily coupled as sodium salts with a variety of diazotised amines, *o*- and *p*-chlorophenylarsenious oxides could not be made to undergo the reaction with aniline or *o*-chloroaniline, the only products isolated being the corresponding chlorophenylarsonic acids, formed by oxidation of the oxides.

Many of the diarylchloroarsines, AsRR'Cl, required for conversion into the cyanoarsines were obtained from these diarylarsonous acids by reduction with sulphur dioxide in the presence of hydrochloric acid, but a few of the symmetrical ones were prepared by heating the appropriate aryldichloroarsine, $AsRCl_2$, with three molecular proportions of the corresponding arylarsenious oxide (the Pope–Turner process). The method of Steinkopf (*Annalen*, 1917, **413**, 310), using 2-thienylmercury chloride and arsenic trichloride, has been modified to give more satisfactory yields of di-2-thienylchloroarsine, and *phenyl-2-thienylchloroarsine* has been prepared, first from 2-thienylmercury chloride and phenyldichloroarsine, and secondly from phenylmercury chloride and 2-thienyldichloroarsine. The diarylcyanoarsines were obtained from the chloroarsines by the action of sodium cyanide.

p-*Phenylenebisdichloroarsine*, $C_6H_4(AsCl_2)_2$, has been prepared by reduction of *p*-phenylenediarsonic acid with sulphur dioxide in the presence of hydrogen chloride.

EXPERIMENTAL.

Diarylarsonous Acids.

***Di*-m-*tolylarsonous Acid*.**—The following procedure is based upon a method developed before 1940 at the Ministry of Supply Research Establishment, Sutton Oak, for the preparation of diphenylarsonous acid. *m*-Toluidine (21·8 g.) in concentrated hydrochloric acid (42·5 c.c.) and water (85 c.c.), was diazotised below 0° by the addition of sodium nitrite (14·7 g.) in water (45 c.c.), and the solution made neutral to Congo-red with concentrated aqueous sodium carbonate. Meanwhile *m*-tolylarsenious oxide (37 g.) was dissolved by warming with aqueous sodium hydroxide (23 c.c. of 36·7%) and water (30 c.c.), and the solution diluted with more water (730 c.c.) and filtered. The diazo-solution was kept below 0° and mechanically stirred while the arsenious oxide solution was added dropwise below the surface during 2 hours, a little nitrobenzene being added occasionally to dispel the froth. Stirring was then continued for a further 2 hours below 0°, after which the mixture was left overnight. Aqueous sodium hydroxide (8 c.c. of 36·7%) was added, the whole stirred for an hour, the tarry material removed by filtration, and the filtrate stirred with charcoal for 20 minutes at room temperature. After being again filtered, the

* By a recent decision the oxyacids of phosphorus, arsenic, and antimony are now named as in the following examples:

$PRO(OH)_2$	$PR(OH)_2$	$PR_2O·OH$	$PR_2·OH$
Phosphonic	Phosphinic	Phosphonous	Phosphinous

The compounds AsRR'O·OH, which under I.U.C. Rule 34 would be called arsinic acids, are therefore here called arsonous acids.—Editor.

solution was treated with ice, and acidified (Congo-red) with concentrated hydrochloric acid. The precipitate (8 g.) was crystallised from aqueous alcohol, from which *di*-m-*tolylarsonous acid* separated in colourless needles, m. p. 140—143° (Found : C, 57·7; H, 5·2. $C_{14}H_{15}O_3As$ requires C, 57·9; H, 5·2%).

The following were prepared by a similar process, the starting materials which were used being indicated, where necessary, by giving the amine. The yields were generally between 10% and 30% of the theoretical, but no figures are given because several of the preparations have been made only once, and adjustment of the conditions would no doubt give improved results : *phenyl*-o-*tolylarsonous acid* (from *o*-toluidine), colourless prisms, m. p. 163°, from aqueous alcohol (Found : C, 55·5; H, 4·6. $C_{13}H_{13}O_3As$ requires C, 56·5; H, 4·7%); *phenyl*-m-*tolylarsonous acid* (from *m*-toluidine), colourless prisms, m. p. 117—119°, from aqueous alcohol (Found : C, 54·9; H, 4·6%); *phenyl*-m-4-*xylylarsonous acid* (from *m*-4-xylidine), colourless needles, m. p. 165—167°, from water (Found : C, 58·1; H, 5·4%); *di*-o-*tolylarsonous acid*, colourless prisms, m. p. 197°, from alcohol (Found : C, 57·0; H, 5·0%); o-*tolyl*-m-*tolylarsonous acid* (from *m*-toluidine), colourless plates, m. p. 129—131°, from aqueous alcohol (Found : C, 56·7; H, 5·2%); *o*-tolyl-*p*-tolylarsonous acid (from *o*-toluidine); m-*tolyl*-p-*tolylarsonous acid* (from *m*-toluidine), yellow prisms, m. p. 145—146°, from aqueous alcohol (Found : C, 58·2; H, 5·2%); di-*p*-tolylarsonous acid, m. p. 171° (cf. La Coste, *Annalen*, 1881, **208**, 1; Matsumiya and Nakai, *Chem. Zentr.*, 1926, i, 652; 1927, i, 1302); o-*tolyl*-m-4-*xylylarsonous acid* (from *m*-4-xylidine), colourless needles, m. p. 184—185°, from aqueous alcohol (Found : C, 58·3; H, 5·4. $C_{15}H_{17}O_3As$ requires C, 59·2; H, 5·6%); p-*tolyl*-m-4-*xylylarsonous acid* (from *m*-4-xylidine), colourless needles, m. p. 138—140°, from aqueous alcohol (Found : C, 58·2; H, 5·5%); *2-chlorodiphenylarsonous acid* (from *o*-chloroaniline), m. p. 184—186° (Found : C, 48·4; H, 3·7. $C_{12}H_{10}O_2ClAs$ requires C, 48·6; H, 3·4%); 4-chlorodiphenylarsonous acid (from *p*-chloroaniline), m. p. 161° (Found : C, 48·0; H, 3·4%) (cf. Mann and Watson, *J.*, 1947, 505); o-*chlorophenyl*-o-*tolylarsonous acid* (from *o*-chloroaniline), colourless prisms, m. p. 218—224°, from aqueous alcohol (Found : C, 50·9; H, 4·2. $C_{13}H_{12}O_2ClAs$ requires C, 50·2; H, 3·9%); p-*chlorophenyl*-o-*tolylarsonous acid* (from *p*-chloroaniline), colourless prisms, m. p. 131—134°, from acetone (Found : C, 49·0; H, 3·5%); o-*chlorophenyl*-p-*tolylarsonous acid* (from *o*-chloroaniline), colourless prisms, m. p. 170—172°, from aqueous alcohol (Found : C, 50·1; H, 4·0%); m-*chlorophenyl*-p-*tolylarsonous acid* (from *m*-chloroaniline), colourless prisms, m. p. 124—125°, from aqueous alcohol (Found : C, 49·8; H, 4·0%); p-*chlorophenyl*-p-*tolylarsonous acid* (from *p*-chloroaniline), colourless needles, m. p. 144°, from aqueous alcohol (Found : C, 50·2; H, 3·9%); p-*nitrophenyl*-p-*tolylarsonous acid* (from *p*-nitroaniline), colourless needles, m. p. 142—144°, from water (Found : C, 48·5; H, 3·9. $C_{13}H_{12}O_4NAs$ requires C, 48·6; H, 3·7%); 3-*formyldiphenylarsonous acid* (from *m*-aminobenzaldehyde), colourless prisms, m. p. 168° (softens at 163°), from water (Found : C, 52·4; H, 4·0. $C_{13}H_{11}O_3As$ requires C, 53·8; H, 3·8%) [its 2 : 4-*dinitrophenylhydrazone* separated from alcohol in yellow prisms, m. p. 270° (decomp.) (Found : N, 12·1. $C_{19}H_{15}O_6N_4As$ requires N, 11·9%)]; 3-*acetyldiphenylarsonous acid* (from *m*-aminoacetophenone), colourless needles, m. p. 146—148°, from aqueous alcohol (Found : C, 55·4; H, 4·4. $C_{14}H_{13}O_3As$ requires C, 55·3; H, 4·3%); 3-*carboxydiphenylarsonous acid* (from *m*-aminobenzoic acid), yellow prisms, m. p. 215° (decomp.), from aqueous alcohol (Found : C, 51·3; H, 3·6. $C_{13}H_{11}O_4As$ requires C, 51·0; H, 3·6%); 4-*carboxydiphenylarsonous acid* (from *p*-aminobenzoic acid), almost colourless needles, m. p. 229—231°, from aqueous alcohol (Found : C, 51·2; H, 3·8%); phenyl-1-naphthylarsonous acid (from α-naphthylamine), m. p. 181—183° (cf. Blicke and Smith, *J. Amer. Chem. Soc.*, 1929, **51**, 3479; Klippel, *Chem. Zentr.*, 1931, i, 1440); *phenyl*-2-*naphthylarsonous acid* (from β-naphthylamine), m.p. 157—159° (Found : C, 58·6; H, 4·3. $C_{16}H_{13}O_2As$ requires C, 61·5; H, 4·2%); p-*tolyl*-1-*naphthylarsonous acid* (from α-naphthylamine), colourless plates, m. p. 198—200°, from aqueous alcohol (Found : C, 62·4; H, 4·8. $C_{17}H_{15}O_2As$ requires C, 62·6; H, 4·6%); p-*tolyl*-2-*naphthylarsonous acid* (from β-naphthylamine), pale pink prisms, m. p. 160—162°, from aqueous alcohol (Found : C, 62·6; H, 4·6%).

m-*Chlorophenyl*-o-*tolylarsonous Acid*.—The following process was based upon conditions developed by Professor A. R. Todd in 1940 for diphenylarsonous acid, and communicated by the Ministry of Supply. A suspension of the hydrochloride of *m*-chloroaniline (25 g. of the base) in concentrated hydrochloric acid (45 c.c.) was cooled to −15° by the addition of ice, and diazotised below 0° by the gradual addition of sodium nitrite (14 g.) during 15 minutes. The solution was then made just neutral to Congo-red with aqueous sodium carbonate. *o*-Tolylarsenious oxide (35·7 g.) was dissolved in 10% sodium hydroxide solution (125 c.c.), and water added to make the volume up to 250 c.c. The diazo- and oxide solutions were added simultaneously below the surface to a solution of Lissapol LS (1 g.) in water (50 c.c.) immersed in an ice-bath and vigorously stirred. The diazo-solution was added slightly in advance of the oxide solution, and during the process, which was completed in about 1½ hours, the temperature was kept at 0°. A few drops of nitrobenzene were added to prevent excessive frothing, and the mixture was kept slightly alkaline to brilliant-yellow paper by addition of sodium carbonate solution as necessary. Sodium carbonate (10 g.) was then added in portions during 1 hour, and stirring continued, still with an ice-bath, until the presence of the diazo-compound could no longer be detected by means of H-acid. The solution was filtered to remove a considerable amount of tarry material, stirred for some time with charcoal, and again filtered. On acidification (to Congo-red) with hydrochloric acid, m-*chlorophenyl*-o-*tolylarsonous acid* (11 g.) was precipitated as a gum, but this crystallised after a few hours. After crystallisation from aqueous alcohol, it was obtained in colourless prisms, m. p. 138° (Found : C, 50·1; H, 3·8%).

The following were prepared by a process similar to the above : o-*nitrophenyl*-o-*tolylarsonous acid* (from *o*-nitroaniline), pale yellow prisms, m. p. 220—221° (with darkening), from alcohol (Found : C, 48·6; H, 3·8%); m-*nitrophenyl*-o-*tolylarsonous acid* (from *m*-nitroaniline), colourless prisms, m. p. 183—186°, from water (Found : C, 48·6; H, 3·9%); p-*nitrophenyl*-o-*tolylarsonous acid* (from *p*-nitroaniline), colourless prisms, m. p. 169—171°, from alcohol (Found : C, 48·6; H, 3·9%).

2-*Acetamidodiphenylarsonous Acid*.—A solution of 2-nitrodiphenylarsonous acid (45 g., prepared by the method of Sakellarios, *Ber.*, 1924, **57**, 1514) and sodium hydroxide (35 g.) in water (450 c.c.) was added in a thin stream to a suspension of ferrous hydroxide prepared by adding sodium hydroxide (110 g. in 400 c.c. of water) to a rapidly stirred solution of ferrous sulphate (255 g.) in water (700 c.c.). After the mixture had been stirred for 3 hours, it was left for a day and then filtered. The filtrate was

mechanically stirred and treated gradually with hydrochloric acid (12%) until it became turbid. A few c.c. of dilute acetic acid were then added, and the gummy pink precipitate was filtered off. This process was repeated with further successive small amounts of acetic acid until a crystalline precipitate began to form. The precipitation of 2-aminodiphenylarsonous acid (25 g., m. p. 129—130°; cf. Kalb, *Annalen*, 1921, **423**, 39) was then completed by addition of excess of acetic acid. A mixture of the amino-acid (10 g.), acetic anhydride (20 c.c.), acetic acid (100 c.c.), and concentrated sulphuric acid (0·5 c.c.) was heated on a steam-bath for an hour, and most of the volatile material then removed by distillation under reduced pressure. When water was added and the solution concentrated to small bulk, *2-acetamidodiphenylarsonous acid* (8 g.) separated. After crystallisation from alcohol (charcoal), it melted at 193—195° (Found: C, 52·1; H, 4·5; N, 4·4. $C_{14}H_{14}O_3NAs$ requires C, 52·7; H, 4·4; N, 4·4%).

Diarylchloroarsines.

2-Chlorodiphenylchloroarsine.—2-Chlorodiphenylarsonous acid (15 g.) was suspended in concentrated hydrochloric acid (30 c.c.) at 90°, a crystal of potassium iodide was added, and sulphur dioxide was passed through with mechanical stirring for 2 hours. When cold, the oily product was extracted with carbon tetrachloride, and the extract dried (Na_2SO_4). After the solvent had been removed by distillation from a water-bath under reduced pressure, *2-chlorodiphenylchloroarsine* remained as an oil which solidified on being cooled in a freezing mixture. It then melted at 30—35° (Found: hydrolysable Cl, 12·6. $C_{12}H_9Cl_2As$ requires hydrolysable Cl, 11·9%).

The following were similarly prepared from the corresponding derivatives of diphenylarsonous acid: *o-nitrophenyl-o-tolylchloroarsine*, yellow prisms, m. p. 93—96°, from petroleum (b. p. 60—80°) (Found: N, 4·4; Cl, 10·7. $C_{13}H_{11}O_2NClAs$ requires N, 4·3; Cl, 11·0%); *p-nitrophenyl-p-tolylchloroarsine*, yellow needles, m. p. 94—96°, from methyl alcohol (Found: Cl, 9·2%); *3-acetyldiphenylchloroarsine*, colourless prisms, m. p. 71—72°, from petroleum (b. p. 60—80°) (Found: Cl, 11·6. $C_{14}H_{12}OClAs$ requires Cl, 11·6%); *diphenylchloroarsine-3-carboxylic acid*, colourless prisms, m. p. 134—136°, from benzene (Found: Cl, 10·6. $C_{13}H_{10}O_2ClAs$ requires Cl, 11·5%); *diphenylchloroarsine-4-carboxylic acid*, colourless prisms, m. p. 115—117°, from benzene–petroleum (b. p. 60—80°) (Found: Cl, 10·7%); *2-acetamidodiphenylchloroarsine* (prepared at room temperature), colourless needles, m. p. 162—164°, from benzene (Found: C, 53·3; H, 4·2; Cl, 10·6. $C_{14}H_{13}ONClAs$ requires C, 52·3; H, 4·0; Cl, 11·0%). A number of other derivatives of diphenylchloroarsine were formed by a similar process as intermediates in the preparation of the cyanoarsines described below, but were not characterised.

Methyl Diphenylchloroarsine-3-carboxylate.—After diphenylchloroarsine-3-carboxylic acid (5 g.) had been refluxed for 10 hours with methyl alcohol (50 c.c.) saturated with hydrogen chloride, the solvent was removed by distillation under reduced pressure until frothing became troublesome. The residue was dissolved in warm benzene, and the solution dried ($MgSO_4$), boiled for 10 minutes with charcoal, filtered, and evaporated under reduced pressure. The *ester* was obtained as a brown oil (Found: C, 52·4; H, 4·1; Cl, 10·7. $C_{14}H_{12}O_2ClAs$ requires C, 52·1; H, 3·7; Cl, 11·0%). *Methyl diphenylchloroarsine-4-carboxylate* was similarly prepared and obtained as a pale brown oil (Found: C, 52·8; H, 4·0; Cl, 9·8%).

Di-o-chlorophenylchloroarsine.—The following conditions are based upon the Pope–Turner process for diphenylchloroarsine, communicated by the Ministry of Supply. A mixture of *o*-chlorophenyldichloroarsine (5·2 g.) and *o*-chlorophenylarsenious oxide (12·3 g.) was heated at 300° for an hour in an atmosphere of carbon dioxide, cooled, and treated with benzene. After removal of arsenious oxide by filtration, the benzene was distilled off under reduced pressure in an atmosphere of hydrogen. The residual *di-o-chlorophenylchloroarsine* solidified on cooling and, after crystallisation from petroleum, melted at 73—75° (Found: hydrolysable Cl, 10·3. $C_{12}H_8Cl_2As$ requires C, 43·2; H, 2·4; hydrolysable Cl, 10·6%).

The following were prepared by a similar process: di-*p*-chlorophenylchloroarsine, m. p. 45—48°, after being distilled and collected at 175—179°/0·6 mm. (Found: C, 43·4; H, 2·1; hydrolysable Cl, 10·4%) (cf. Hunt and Turner, *J.*, 1925, **127**, 2667); di-1-naphthylchloroarsine, m. p. 163—165° (cf. Challenger and Ridgway, *J.*, 1922, **121**, 104; Matsumiya and Nakai, *loc. cit.*; Blicke and Smith, *J. Amer. Chem. Soc.*, 1929, **51**, 1558); *di-2-naphthylchloroarsine*, colourless plates, m. p. 88°, from petroleum (b. p. 60—80°) (Found: Cl, 10·1. $C_{20}H_{14}ClAs$ requires Cl, 9·7%).

3-Chloroacetyldiphenylchloroarsine.—3-Acetyldiphenylchloroarsine was heated at 100° in a sealed tube with slightly more than one molecular proportion of chlorine in dry carbon tetrachloride solution in bright sunlight for several hours. After removal of the solvent under reduced pressure, *3-chloroacetyldiphenylchloroarsine* remained as a viscous yellow oil (Found: hydrolysable Cl, 21·0. $C_{14}H_{11}OCl_2As$ requires hydrolysable Cl, 20·8%).

Di-2-thienylchloroarsine.—The following conditions proved to be much more satisfactory for this preparation than those described by Steinkopf (*loc. cit.*). A mixture of 2-thienylmercury chloride (600 g.), arsenic trichloride (180 g.), and toluene (1100 c.c.) was refluxed for 6 hours, cooled, and filtered from the precipitate of mercuric chloride. Most of the toluene and unchanged arsenic trichloride were removed from the filtrate by distillation under reduced pressure in an atmosphere of hydrogen from a flask fitted with a fractionating column. The residual oil (248 g.) was fractionally distilled (hydrogen atmosphere) at 13 mm. in seven separate portions to avoid prolonged heating and consequent disproportionation of the product. The following combined fractions were collected: (i) b. p. below 120° (13 g.), (ii) b. p. 120—125° (7·5 g., mostly 2-thienyldichloroarsine), (iii) b. p. 125—180° (36 g.), and (iv) b. p. 180—220° (130 g.). The last fraction, most of which boiled at 195—210°/13 mm., was a reasonably pure specimen of di-2-thienylchloroarsine (Found: Cl, 11·8. Calc. for $C_8H_6S_2ClAs$: Cl, 12·8%). The residue was distilled at a lower pressure and gave an oil (40 g.), b. p. 195—200°/0·5 mm., which was mainly tri-2-thienylarsine.

For the preparation of purer tri-2-thienylarsine, a mixture of 2-thienyldichloroarsine and di-2-thienylchloroarsine was heated in toluene for 7 hours under reflux with excess of 2-thienylmercury chloride, and worked up as described above. A fraction, b. p. 180—194°/0·8 mm., containing 5·5% of chlorine,

and another, b. p. 194—196°/0·8 mm., containing 0·8% of chlorine, were collected. These were united and heated for 5 minutes in alcohol at 70° with a little potassium hydroxide. After filtration, the alcohol was removed by distillation in steam, and the oily residue was washed by decantation with water and dissolved in ether. The solution was dried (Na_2SO_4), the solvent removed, and the residue fractionally distilled in an atmosphere of hydrogen. Tri-2-thienylarsine, almost free from chlorine, was collected at 193—198°/0·55 mm. as a practically colourless liquid (Found: C, 44·4; H, 3·1; Cl, 0·4; S, 31·2; As, 20·5. Calc. for $C_{12}H_9S_3As$: C, 44·4; H, 2·8; S, 29·7; As, 23·2%).

Phenyl-2-thienylchloroarsine.—(*a*) A mixture of 2-thienylmercury chloride (10 g.), phenyldichloroarsine (7 g.), and toluene (20 c.c.) was boiled under reflux for 7 hours. After the solid which had separated had been removed by filtration and washed with toluene, the solvent was removed from the united toluene solutions under reduced pressure. The residue was distilled at a low pressure in an atmosphere of hydrogen, and two main fractions were collected. The first (1·7 g.), b. p. 93—106°/0·3 mm., was evidently phenyldichloroarsine, 2-thienyldichloroarsine, or a mixture of the two (Found: Cl, 32·0. Calc. for $C_6H_5Cl_2As$: Cl, 31·8. Calc. for $C_4H_3Cl_2SAs$: Cl, 31·0%). The second (3·5 g.) was collected at 158—172°/0·9 mm., and consisted essentially of *phenyl-2-thienylchloroarsine* (Found: C, 42·0; H, 2·9; Cl, 15·9. $C_{10}H_8ClSAs$ requires C, 44·4; H, 3·0; Cl, 13·1%). A small amount of less volatile material remained.

(*b*) A mixture of phenylmercury chloride (27 g., prepared as described by Roeder and Blasi, *Ber.*, 1914, **47**, 2748), 2-thienyldichloroarsine (19·5 g.), and toluene (50 c.c.) was boiled under reflux for 7 hours, and then treated as above. After a fraction (7 g.) of dichloroarsine type (Found: Cl, 31·4%) had been obtained at 96—112°/0·65 mm., phenyl-2-thienylchloroarsine (6 g.) was collected at 150—156°/0·7 mm. (Found: C, 41·0; H, 2·6; Cl, 15·3%). The analyses indicate a small amount of disproportionation to dichloroarsines during distillation.

Diarylcyanoarsines.

Some of the cyanoarsines described below were isolated as solids and were purified by crystallisation, but those obtained as oils were usually not distilled owing to the possibility of disproportionation in accordance with the scheme, $2R_2As{\cdot}CN \rightleftarrows RAs(CN)_2 + R_2As$. Most of these liquids were shown by analysis to be reasonably pure, but, in a few, a low nitrogen content probably indicated the presence of a small amount of the corresponding oxide, RR'As·O·AsRR', formed by hydrolysis.

Phenyl-o-tolylcyanoarsine.—Phenyl-*o*-tolylchloroarsine (15 g.) was added to a solution of sodium cyanide (2·9 g.) in water (6 c.c.), and the whole shaken vigorously for 10 minutes, the temperature being maintained at 60°. The resulting oil was extracted with ether, and, after the extract had been dried (Na_2SO_4) and filtered, the solvent was removed by distillation under reduced pressure from a water-bath. *Phenyl-o-tolylcyanoarsine* (11 g.) remained as a faintly red, viscous oil (Found: C, 61·9; H, 4·2; N, 5·2. $C_{14}H_{12}NAs$ requires C, 62·5; H, 4·5; N, 5·2%).

The following were similarly prepared: *phenyl-p-tolylcyanoarsine*, golden yellow liquid (Found: C, 63·2; H, 4·8; N, 4·7%); *2-chlorodiphenylcyanoarsine*, pale yellow oil, which solidified on standing and then melted at 40—42° (Found: C, 54·7; H, 3·4; N, 4·9. $C_{13}H_9NClAs$ requires C, 53·9; H, 3·1; N, 4·8%); *4-chlorodiphenylcyanoarsine*, m. p. 102° (Found: N, 4·8%); *phenyl-2-thienylcyanoarsine*, practically colourless oil, b. p. 168—174°/0·5 mm., which solidified on standing and then melted at 49—51° (Found: C, 49·5; H, 3·1; N, 4·4; S, 12·8. $C_{11}H_8NSAs$ requires C, 50·6; H, 3·1; N, 5·4; S, 12·3%).

Di-m-tolylcyanoarsine.—A suspension of di-*m*-tolylarsonous acid (7 g.) in concentrated hydrochloric acid (40 c.c.) at 90°, containing a little potassium iodide, was mechanically stirred while sulphur dioxide was passed in for 1½ hours. The oily di-*m*-tolylchloroarsine was extracted with carbon tetrachloride, and the extract dried ($MgSO_4$) and evaporated on the steam-bath under reduced pressure. The residue was dissolved in benzene (20 c.c.) and shaken with sodium cyanide (1·7 g.) in water (3·4 c.c.) at 40° for 10 minutes. The whole was filtered from sodium chloride, the aqueous layer removed, and the benzene solution dried ($MgSO_4$). When the benzene was removed on the steam-bath under reduced pressure, *di-m-tolylcyanoarsine* remained in good yield as a brownish yellow oil (Found: N, 5·0. $C_{15}H_{14}NAs$ requires N, 4·9%). The oil solidified on standing, and then melted again at 43—47°.

The following were similarly prepared: *phenyl-m-tolylcyanoarsine*, brownish yellow liquid (Found: N, 5·1%); *phenyl-m-4-xylylcyanoarsine*, viscous brown oil (Found: N, 4·6%); *di-o-tolylcyanoarsine*, colourless prisms, m. p. 74°, from petroleum (b. p. 40—60°) (Found: N, 5·2%); *o-tolyl-m-tolylcyanoarsine*, pale brown oil (Found: N, 4·1%); *o-tolyl-p-tolylcyanoarsine*, pale brown oil which solidified on standing (Found: C, 61·9; H, 4·8; N, 4·5. $C_{15}H_{14}NAs$ requires C, 63·6; H, 4·9%); *m-tolyl-p-tolylcyanoarsine*, reddish brown oil (Found: N, 4·5%); *di-p-tolylcyanoarsine*, colourless plates, m. p. 62°, with a faint pink tinge, from petroleum (b. p. 40—60°) (Found: N, 5·0%); *o-tolyl-m-4-xylylcyanoarsine*, brown oil (Found: N, 3·5. $C_{16}H_{16}NAs$ requires N, 4·7%); *p-tolyl-m-4-xylylcyanoarsine*, brown oil (Found: N, 3·7%); *o-chlorophenyl-o-tolylcyanoarsine*, colourless prisms, m. p. 69°, from petroleum (b. p. 40—60°) (Found: N, 4·5. $C_{14}H_{11}NClAs$ requires N, 4·6%); *m-chlorophenyl-o-tolylcyanoarsine*, colourless prisms, m. p. 61°, from petroleum (b. p. 40—60°) (Found: N, 4·8%); *p-chlorophenyl-o-tolylcyanoarsine*, colourless prisms, m. p. 64°, from petroleum (b. p. 40—60°) (Found: N, 4·8%); *o-chlorophenyl-p-tolylcyanoarsine*, brown oil (Found: N, 4·2%); *m-chlorophenyl-p-tolylcyanoarsine*, brown oil (Found: N, 4·2%); *p-chlorophenyl-p-tolylcyanoarsine*, brownish yellow oil (Found: N, 4·4%); *o-nitrophenyl-o-tolylcyanoarsine*, yellow prisms, m. p. 105—107°, from petroleum (b. p. 60—80°) (Found: N, 7·6. $C_{14}H_{11}O_2N_2As$ requires N, 8·9%); *m-nitrophenyl-o-tolylcyanoarsine*, colourless prisms, m. p. 99—101°, from benzene (Found: N, 8·9%); *p-nitrophenyl-o-tolylcyanoarsine*, colourless prisms, m. p. 103—105°, from benzene (Found: N, 8·9%); *p-nitrophenyl-p-tolylcyanoarsine*, pale yellow needles, m. p. 88—90°, from petroleum (b. p. 60—80°) (Found: N, 8·8%); *3-formyldiphenylcyanoarsine*, viscous, golden yellow oil (Found; N, 4·6. $C_{14}H_{10}ONAs$ requires N, 4·9%); *3-acetyldiphenylcyanoarsine*, colourless prisms, m. p. 57—59°, from petroleum (Found: CN, 8·8. $C_{15}H_{12}ONAs$ requires CN, 8·8%); phenyl-1-naphthylcyanoarsine, yellow plates, m. p. 98—99°, from methyl alcohol (Found: N, 3·9%) (cf. Klippel, *loc. cit.*); *phenyl-2-naphthylcyanoarsine*, m. p. 59—61°, after crystallisation from petroleum

(b. p. 60—80°) (Found : N, 4·5. $C_{17}H_{12}NAs$ requires N, 4·6%); p-*tolyl*-1-*naphthylcyanoarsine*, colourless prisms, m. p. 83—84°, from benzene–petroleum (b. p. 60—80°) (Found : N, 4·4. $C_{18}H_{14}NAs$ requires N, 4·4%); p-*tolyl*-2-*naphthylcyanoarsine*, colourless prisms, m. p. 99°, from petroleum (b. p. 60—80°) (Found : N, 4·4%).

Di-o-*chlorophenylcyanoarsine*.—A solution of di-*o*-chlorophenylchloroarsine in the minimum quantity of benzene at 40° was vigorously shaken for 10 minutes at 50° with slightly more than one molecular proportion of sodium cyanide in concentrated aqueous solution. After the mixture had been cooled, sufficient water and benzene were added to give two clear layers. The benzene layer was washed with water, dried ($MgSO_4$), and filtered. When the solvent had been removed under reduced pressure in an atmosphere of hydrogen, *di*-o-*chlorophenylcyanoarsine* remained as an oil which soon solidified. After crystallisation from petroleum (b. p. 60—80°), it melted at 85—87° (Found : N, 4·1. $C_{13}H_8NCl_2As$ requires N, 4·3%).

The following were similarly prepared : *di*-p-*chlorophenylcyanoarsine*, b. p. 198—200°/0·5 mm., colourless prisms, m. p. 58—60°, from petroleum (b. p. 60—80°) (Found : CN, 7·6. $C_{13}H_8NCl_2As$ requires CN, 8·0%); *methyl diphenylcyanoarsine*-3-*carboxylate*, pale brown oil (Found : N, 3·6. $C_{15}H_{12}O_2NAs$ requires N, 4·5%); *methyl diphenylcyanoarsine*-4-*carboxylate*, pale brown oil (Found : N, 3·9%); di-1-naphthylcyanoarsine, colourless plates, m. p. 191°, from benzene (Found : N, 4·2%) (cf. Grichkiewitch-Trochimowski, Mateyak, and Zablotski, *Bull. Soc. chim.*, 1927, **41**, 1323); *di*-2-*naphthylcyanoarsine*, colourless prisms, m. p. 89—91°, from benzene–petroleum (b. p. 60—80°) (Found : N, 3·8. $C_{21}H_{14}NAs$ requires N, 3·9%).

2-*Aminodiphenylcyanoarsine*.—After a solution of 2-aminodiphenylarsonous acid (5 g.) in concentrated hydrochloric acid (100 c.c.) had been saturated with sulphur dioxide, the precipitated hydrochloride of 2-aminodiphenylchloroarsine (5·5 g.) was collected on a sintered glass filter, washed with hydrochloric acid, and dried. The hydrochloride (3·2 g.) was triturated for a few minutes with a cold solution of sodium cyanide (1·05 g.) in water (3 c.c.). A little benzene was added and trituration continued until the cyanoarsine had dissolved in the benzene layer, which was then separated, dried ($MgSO_4$), and evaporated under reduced pressure at room temperature. 2-*Aminodiphenylcyanoarsine* melted at 53° after recrystallisation from benzene, and was found to be hygroscopic (Found : CN, 8·9. $C_{13}H_{11}N_2As$ requires CN, 9·6%).

Di-m-*aminophenylcyanoarsine*.—When sulphur dioxide was passed into a solution of di-*m*-aminophenylarsonous acid (prepared as described by Blicke, Oakdale, and Oneto, *J. Amer. Chem. Soc.*, 1934, **56**, 141) in concentrated hydrochloric acid containing a little sodium iodide, the dihydrochloride of di-*m*-aminophenylchloroarsine was precipitated in almost quantitative yield. Sodium cyanide (3·1 molecular proportions) was added in small portions to a well-stirred suspension of the dihydrochloride in slightly more than its own weight of water below 30°. The mixture was diluted with its own volume of water, and stirring was continued for a further 5 minutes. The solid *di*-m-*aminophenylcyanoarsine* was filtered off, washed with water, and dried in a desiccator. After crystallisation from benzene, it was obtained in colourless plates, m. p. 114° (Found : CN, 9·3. $C_{13}H_{12}N_3As$ requires CN, 9·1%).

Di-2-*thienylcyanoarsine*.—Di-2-thienylchloroarsine (50 g.) was added in portions with vigorous shaking to a solution of sodium cyanide (10·5 g.) in water (21 c.c.), the temperature being kept between 17° and 25°. After the completion of the reaction, indicated by a fall in temperature, benzene (250 c.c.) was added, and the mixture filtered to remove sodium chloride. The benzene layer was shaken with an equal volume of water, dried ($MgSO_4$), and filtered. After the solvent had been removed from the filtrate, the residue was distilled under reduced pressure in an atmosphere of hydrogen. *Di*-2-*thienylcyanoarsine* (32 g.) was collected as an oil, b. p. 175—200°/0·3 mm., which rapidly solidified. On crystallisation from petroleum (b. p. 40—60°) it was obtained in colourless plates, m. p. 51—55° (Found : C, 39·3; H, 2·3; N, 5·2. $C_9H_6NS_2As$ requires C, 40·4; H, 2·2; N, 5·2%).

Arsanthren Cyanide, $C_6H_4<[AsCN]_2>C_6H_4$.—A mixture of arsanthren chloride (prepared from *o*-arsanilic acid as described by Kalb, *loc. cit.*) with 10 times its weight of dry toluene and freshly precipitated silver cyanide (50% excess) was refluxed for 10 hours. When the hot solution was filtered and left to cool, *arsanthren cyanide* separated. After recrystallisation from benzene, it was obtained in large, colourless prisms (dried under reduced pressure at room temperature) containing benzene of crystallisation (Found : C, 52·1; H, 2·7; N, 7·3. $2C_{14}H_8N_2As_2,C_6H_6$ requires C, 51·9; H, 2·8; N, 7·1%). When heated to constant weight under reduced pressure at 110—120°, the loss in weight amounted to 9·8% (Calc. : 9·9%), and arsanthren cyanide, m. p. 165—167°, was obtained free from benzene (Found : CN, 15·0. $C_{14}H_8N_2As_2$ requires CN, 14·7%).

p-*Phenylenebisdichloroarsine*.—Crude *p*-phenylenediarsonic acid, prepared essentially as described by Bart (*Annalen*, 1922, **429**, 55), was dissolved in hot alcohol which had been saturated with hydrogen chloride. The solution was cooled, filtered, treated with a few c.c. of hydriodic acid (*d* 1·7), saturated with sulphur dioxide, and left at room temperature for 2 days, during which time hydrogen chloride and sulphur dioxide were occasionally passed in. A small amount, m. p. 93—97°, of practically pure p-*phenylenebisdichloroarsine* separated and was removed, but the main product (m. p. 75—85°) was obtained by adding the filtrate to about an equal volume of water. After crystallisation from petroleum (b. p. 60—80°), it was obtained in practically colourless plates, m. p. 96—97° (Found : C, 19·9; H, 1·1; Cl, 37·5. $C_6H_4Cl_4As_2$ requires C, 19·6; H, 1·1; Cl, 38·6%). Kretow and Berlin (*Chem. Zentr.*, 1932, i, 3048) apparently used this substance to obtain the disulphide, $C_6H_4(AsS)_2$, but no details of its preparation or physical properties are given.

We are indebted to Sir Robert Robinson for his interest in these investigations, and to the Chief Scientific Officer, Ministry of Supply, for permission to publish the work.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, January 30th*, 1948.]

450. *Union of Aryl Nuclei. Part VII. Reactions with Acyl Peroxides.*

By D. H. Hey and E. W. Walker.

Reactions have been carried out between a number of acyl peroxides and (*a*) benzene and (*b*) pyridine. In the benzene series these reactions frequently provide good preparative methods for diaryl derivatives, but in the pyridine series the reaction is not one of general applicability, probably owing to the formation of pyridine oxide. Reactions are also described between benzoyl peroxide and (*a*) quinoline and (*b*) 2 : 2 : 4-trimethylpentane, between phthalic acid peroxide and nitrobenzene, and between *m*-nitrobenzoyl peroxide and molten benzoic acid. It is shown that when 1-methyl hydrogen 4-nitrophthalate is converted into a peroxide, by formation of the acid chloride and treatment with hydrogen peroxide, a mixture of two isomerides is obtained. The reactions of the peroxides conform to the free-radical mechanism put forward in an earlier communication (*J.*, 1934, 1966).

Lippmann (*Monatsh.*, 1886, **7**, 521) obtained diphenyl by heating benzoyl peroxide in benzene at 140°, but since he also obtained the same hydrocarbon by thermal decomposition of the peroxide admixed with sand there was no evidence that the benzene had participated in the reaction. The formation of diphenyl by prolonged boiling of benzoyl peroxide in benzene was also observed by Orndorff and White (*Amer. Chem. J.*, 1893, **15**, 347). The first clear indication of the course followed in these reactions came from the work of Gelissen and Hermans (*Ber.*, 1925, **58**, 285), who showed that *p*-chlorobenzoyl and *m*-nitrobenzoyl peroxide react with benzene to give only 4-chlorodiphenyl and 3-nitrodiphenyl respectively, and that 4 : 4′-dichlorodiphenyl and 3 : 3′-dinitrodiphenyl were not formed. In subsequent papers these authors were able to substantiate this view beyond all doubt (*Ber.*, 1925, **58**, 476, 479, 764, 984, 2396; 1926, **59**, 662; etc.). From the reaction between benzoyl peroxide and benzene these workers isolated not only benzoic acid, diphenyl, and phenyl benzoate, but also smaller quantities of *p*-terphenyl, quaterphenyl, esters of higher phenols, and resinous products. Further, when benzoyl peroxide was used with toluene or diphenyl, the resulting products were 2- and 4-methyldiphenyl or *p*-terphenyl respectively. These authors interpreted these reactions as follows:

$$(R\cdot CO_2)_2 + R'H \longrightarrow \begin{cases} \xrightarrow{\text{main reaction}} RR' + R\cdot CO_2H + CO_2 \quad \text{(A)} \\ \xrightarrow{\text{side reaction}} RH + R\cdot CO_2R' + CO_2 \quad \text{(B)} \end{cases}$$

Products such as terphenyl and quaterphenyl resulted from the further action of the peroxide on the hydrocarbons initially formed. Overhoff and Tilman (*Rec. Trav. chim.*, 1929, **48**, 993) investigated the reaction of benzoyl peroxide with pyridine and recorded the isolation of 2- and 4-phenylpyridine. The first attempt to apply the reaction to suitable aromatic compounds with the object of investigating the directive influence of substituent groups or atoms in this reaction was made by Hey (*J.*, 1934, 1966), and the results obtained clearly showed that the reaction was not governed by the normal laws for cationoid or anionoid substitution reactions.

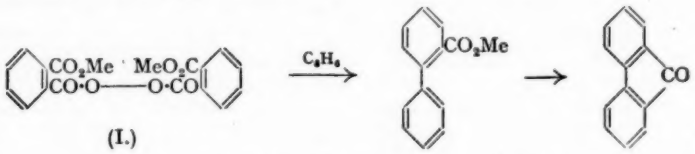
The mechanism of the reaction between acyl peroxides and various organic liquids attracted the attention of Boeseken, Gelissen, and Hermans, but these authors rejected the possibility of the intervention of free radicals (*Annalen*, 1935, **519**, 133; *Rec. Trav. chim.*, 1935, **54**, 760), although they had recognised the marked similarity between certain reactions of the diazo-compounds and the reactions of acyl peroxides (*Ber.*, 1925, **58**, 984). Wieland and Razubaiev (*Annalen*, 1930, **480**, 157) and Wieland, Schapiro, and Metzger (*Annalen*, 1934, **513**, 93) also refused to accept a free radical mechanism mainly on the grounds that in the thermal decomposition of a mixed peroxide, R·CO·O·O·COR′, the product contained only the compound RR′, and RR and R′R′ were absent. These workers maintained that if free radicals were involved all three products would be formed. On the other hand, in the thermal decomposition of the peroxide the two dissimilar radicals R and R′ would probably be produced in close proximity, and being radicals of short life would tend to react together at once according to the Frank–Rabinowitch principle. The view that these reactions involve the participation of free radicals was first put forward by Hey (*loc. cit.*) and later elaborated by Hey and Waters (*Chem. Reviews*, 1937, **21**, 169). The general scheme for the reaction with a compound R′H may be represented as follows:

1. $(R\cdot CO_2)_2 \longrightarrow R\cdot + R\cdot CO_2\cdot + CO_2$
2. $R\cdot + R'H \longrightarrow RR' + H\cdot$
3. $R\cdot + R'H \longrightarrow RH + R'\cdot$
4. $R\cdot CO_2\cdot + R'H \longrightarrow R\cdot CO_2R' + H\cdot$
5. $R\cdot CO_2\cdot + R'H \longrightarrow R\cdot CO_2H + R'\cdot$
6. $R\cdot CO_2\cdot + H\cdot \longrightarrow R\cdot CO_2H$
7. $R\cdot CO_2\cdot + R'\cdot \longrightarrow R\cdot CO_2R'$
8. $R\cdot + H\cdot \longrightarrow RH$
9. $R\cdot + R'\cdot \longrightarrow RR'$

These reactions are accompanied by further reactions between the free radicals and atoms with the products formed in the primary reactions.

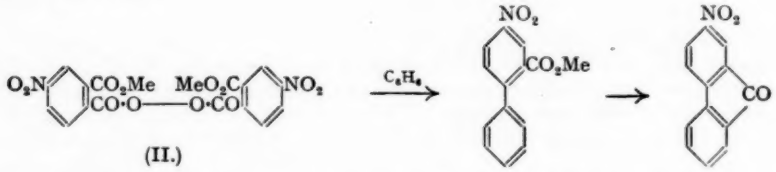
The present communication, which is based on work completed in 1941, the records of which were partly destroyed by enemy action, is mainly directed to the reactions of a number of acyl peroxides with benzene and with pyridine, which were found to follow in general the reaction scheme outlined above. The peroxides used were o-*nitrobenzoyl*, *m*-nitrobenzoyl, *p*-nitrobenzoyl, *p*-chlorobenzoyl, *p*-methoxybenzoyl, 1-naphthoyl, 2-naphthoyl, cinnamoyl, phenylacetyl, 2 : 2′-dicarboxybenzoyl, 2 : 2′-*dicarbomethoxybenzoyl*, 5-*nitro*-2 : 2′-*dicarbomethoxybenzoyl*, and phthaloyl. The peroxides were prepared from the acid chlorides and hydrogen peroxide; *m*-nitrobenzoyl peroxide was also prepared by the nitration of benzoyl peroxide.

In reactions with boiling benzene the three nitrobenzoyl peroxides gave 2-nitrodiphenyl, 3-nitrodiphenyl, and 4-nitrodiphenyl in yields of 60, 80, and 53% respectively, and *p*-methoxybenzoyl peroxide gave 4-methoxydiphenyl in 23% yield. 2-Naphthoyl peroxide gave 2-phenylnaphthalene in 19% yield. The 2 : 2′-dicarbomethoxybenzoyl peroxide (I) reacted readily with boiling benzene to give in 55% yield methyl diphenyl-2-carboxylate, which was identified by hydrolysis and ring closure to give fluorenone:



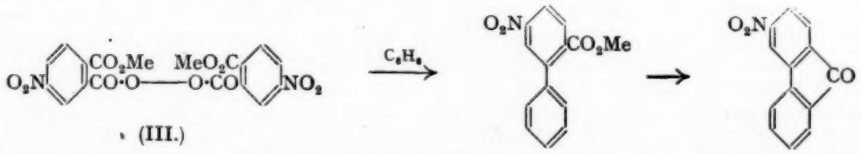
(I.)

The corresponding reaction with the 5-nitro-2 : 2′-dicarbomethoxybenzoyl peroxide was less straightforward. The peroxide obtained in the normal manner from 1-methyl hydrogen 4-nitrophthalate, prepared as described by Wegscheider and Lipschitz (*Monatsh.*, 1900, **21**, 802), proved to be a mixture of two isomerides. The less soluble peroxide of higher melting point underwent reaction with boiling benzene to give 2-methyl hydrogen 4-nitrophthalate and the hitherto unknown *methyl* 4-*nitrodiphenyl*-2-*carboxylate*, identified by hydrolysis and ring closure to give 2-nitrofluorenone. The peroxide of higher melting point must therefore have the constitution (II):



(II.)

The more soluble peroxide of lower melting point could not be obtained entirely free from the isomeric peroxide, and the reaction with benzene gave a mixture of nitrodiphenylcarboxylic esters, which on hydrolysis and ring closure gave a mixture of 2- and 3-nitrofluorenone. The more soluble peroxide must therefore be regarded as having the constitution (III):



(III.)

At the time when this work was completed it was not clear how the peroxide (II) could be formed from 1-methyl hydrogen 4-nitrophthalate, and if the starting material was homogeneous, as claimed by Wegscheider and Lipschitz (*loc. cit.*), it had to be assumed that some rearrangement must have taken place either in the formation of the acid chloride or in the subsequent reactions. In a recent communication (*J. Amer. Chem. Soc.*, 1947, **69**, 1548) Cason has shown that in the conversion of each of the two isomeric half esters of an unsymmetrically substituted dibasic acid into the ester acid chlorides by treatment with thionyl chloride a mixture of the two isomeric acid chlorides is obtained. Ställberg-Stenhagen (*J. Amer. Chem. Soc.*, 1947, **69**, 2568) has studied the conditions under which this type of rearrangement takes place, and considers it likely that it may be due to the intermediate formation of the anhydrides. In the

light of these observations the formation of the two isomeric peroxides from 1-methyl hydrogen 4-nitrophthalate is not unexpected, since the action of thionyl chloride would probably result in the formation of the two isomeric acid chlorides.

No pure products were isolated from the reaction of 1-naphthoyl peroxide or of phthaloyl peroxide with benzene. On the other hand, 2 : 2′-dicarboxybenzoyl peroxide proved to be remarkably stable, and after being boiled with benzene for 120 hours most of it was recovered unchanged. In view of this stability nitrobenzene was chosen as a reactant of higher boiling point. With this solvent reaction took place readily at 140°, and a mixture of 2- and 4-nitrodiphenyl-2′-carboxylic acid was isolated in good yield. The very reactive phenylacetyl peroxide decomposed in benzene solution at 30°, and only dibenzyl, formed by dimerisation of the benzyl radicals, was isolated from the product. This result is in full agreement with that recorded by Kharasch, Kane, and Brown (*J. Amer. Chem. Soc.*, 1942, **64**, 1621), who isolated only dibenzyl and phenylacetic acid from the decomposition of phenylacetyl peroxide in carbon tetrachloride solution. From the reaction between cinnamoyl peroxide and benzene, stilbene was obtained in small yield together with much polymerised material.

The readiness with which peroxides react with aromatic compounds, including nitrobenzene, suggested that in some reactions, especially those carried out at higher temperatures, a secondary reaction might ensue between the peroxide and the aromatic acid formed as a normal product of the main reaction (A). In order to test the extent of this possibility a reaction was carried out between *m*-nitrobenzoyl peroxide and molten benzoic acid at 125°. The acidic products were fractionally precipitated with alkali, and from the least soluble fractions a mixture of nitrodiphenylcarboxylic acids was obtained. From this mixture the hitherto unknown *3-nitrodiphenyl-3′-* and *-4′-carboxylic acids* were isolated. Since neither product could be ring-closed to yield a nitrofluorenone, the only alternative constitution, namely that of 3-nitrodiphenyl-2′-carboxylic acid, is eliminated. In the absence of evidence to the contrary the acid of higher melting point is regarded as having the carboxyl group in the 4′-position. Substitution at the *meta* and *para* positions with respect to the carboxyl group is in agreement with results previously obtained in similar reactions with ethyl benzoate (Hey, *J.*, 1934, 1968). A small quantity of nitrobenzene was also isolated (reaction B), together with some 3 : 3′-dinitrodiphenyl. The latter product is possibly due to the localised explosive decompositions in the body of the liquid, which were a characteristic feature of this reaction.

The reaction between benzoyl peroxide and pyridine was investigated by Overhoff and Tilman (*loc. cit.*), who reported the formation of 2- and 4-phenylpyridine only. In view of the close correspondence between the reactions of benzoyl peroxide and those of nitrosoacetanilide and benzene diazohydroxide, which have already been shown to give rise to substitution at all three positions in the pyridine nucleus, it was considered highly probable that in the case of benzoyl peroxide also all three isomerides were formed. A repetition of this reaction gave a mixture of phenylpyridines in 35% yield from which the picrates of 2-, 3-, and 4-phenylpyridine were isolated. The comparatively low yield of phenylpyridines in this reaction is accompanied by a yield of benzoic acid corresponding to 1·2 mols. per mol. of peroxide used. This indicates the occurrence of a secondary reaction of a type which does not arise in the reactions with benzene, and may be due to the formation of pyridine oxide (cf. Meisenheimer, *Ber.*, 1926, **59**, 1848). This tendency was much more marked in later experiments with substituted benzoyl peroxides. For example, when *o*-nitrobenzoyl peroxide was boiled with pyridine, the acidic fraction consisting of *o*-nitrobenzoic acid accounted for 87% of the peroxide used, and no nitrophenylpyridines were isolated. Similar results were obtained when *m*- and *p*-nitrobenzoyl peroxides were used. On the other hand, both *p*-chlorobenzoyl peroxide and *p*-methoxybenzoyl peroxide reacted readily with pyridine at 95°, and gave mixtures of *p*-chlorophenylpyridines and *p*-methoxyphenylpyridines respectively, both in 27% yield. From these mixtures 2- and 4-*p*-chlorophenylpyridine and 2- and 4-*p*-methoxyphenylpyridine were isolated by fractional crystallisation of the picrates. The reactions of 1-naphthoyl peroxide and of 2-naphthoyl peroxide with pyridine gave mixtures of 1-naphthylpyridines and 2-naphthylpyridines in small yield. In the former case only one 1-naphthylpyridine was isolated in pure form as the picrate : in the latter case fractionation of the picrates of the 2-naphthylpyridines gave the three isomeric 2-naphthylpyridine picrates, identical with the three products previously obtained by Elks and Hey (*J.*, 1943, 444) from the reaction between 1-2′-naphthyl-3 : 3-dimethyltriazen and pyridine. The major isomeride in the mixture was also prepared from the reactions between diazotised β-naphthylamine and pyridine, and between nitrosoaceto-β-naphthalide and pyridine. In both reactions with the naphthoyl peroxides a small quantity of naphthalene was also isolated (reaction B). Reactions with

pyridine were also carried out with 2 : 2′-dicarbomethoxybenzoyl peroxide and with cinnamoyl peroxide. In the former case the methyl esters of a mixture of pyridylbenzoic acids were obtained from which two picrates were formed; in the latter case a small quantity of α-stilbazole was isolated from the product.

A reaction between benzoyl peroxide and quinoline at 105° gave a mixture of phenylquinolines, which was treated with picric acid and the resulting complex mixture of picrates submitted to fractional crystallisation. 4-Phenylquinoline picrate and 5-phenylquinoline picrate were isolated and identified, and indications were obtained of the presence of three other isomerides, but none of these was obtained in a form sufficiently pure for unambiguous identification. For reference purposes the seven isomeric phenylquinolines were synthesised. Of these 5- and 7-phenylquinoline, which had not been reported at that time, were prepared from 3-aminodiphenyl by the Skraup reaction. The mixture of 5- and 7-phenylquinolines thus obtained was separated by fractional crystallisation of the picrates. The more soluble isomeride was identified as the picrate of 5-phenylquinoline by mixed melting point with an authentic specimen prepared at about the same time from 1-5′-quinolyl-3 : 3-dimethyltriazen and benzene (Elks and Hey, *loc. cit.*). The second and less soluble *picrate* must therefore be that of the hitherto unknown 7-phenylquinoline.

Some preliminary experiments were also carried out on reactions between acyl peroxides and saturated aliphatic compounds of various types. It was not possible to pursue this work further in 1941, but reference may be made to the reaction of benzoyl peroxide with 2 : 2 : 4-trimethylpentane. This differed from all the preceding reactions with aromatic and heterocyclic compounds in that the product contained a relatively small yield of benzoic acid and a proportionately high yield of benzene, *i.e.*, predominance of reaction B. Some diphenyl and diphenyl-4-carboxylic acid were also isolated, these being formed presumably as the result of secondary reactions. The difference thus revealed in the reactions of benzoyl peroxide with aromatic and aliphatic compounds is in complete accord with the established properties of the phenyl radical (Hey and Waters, *loc. cit.*).

Experimental.

Preparation of Peroxides.—Unless otherwise stated the peroxides were prepared from a solution of the acid chloride (2 mols.) in chloroform by shaking below 4° with aqueous 25% sodium hydroxide (2 mols.) and 20-vol. hydrogen peroxide (1 mol.) according to a modification of the procedure used for the preparation of *p*-chlorobenzoyl peroxide by Gelissen and Hermans (*Ber.*, 1925, **58**, 292). The peroxides were precipitated from the chloroform solution by the addition of methyl alcohol, and many had to be purified by a repetition of this process since the peroxides do not always lend themselves to crystallisation from hot or warm solvents owing to their instability. Because of the explosive nature of the peroxides, analyses for carbon and hydrogen by combustion were generally discarded in favour of the iodometric method used by Boeseken and Gaster (*Rec. Trav. chim.*, 1930, **49**, 102). Similar difficulties with combustion analyses have been previously recorded by Milas and Panagiotakos (*J. Amer. Chem. Soc.*, 1940, **62**, 1878). The general method of preparation is illustrated by the preparation of *o*-nitrobenzoyl peroxide.

o-*Nitrobenzoyl Peroxide.*—A solution of *o*-nitrobenzoyl chloride (100 g.) in chloroform (100 c.c.) was shaken at 2° with 20-vol. hydrogen peroxide (200 c.c.) and 25% aqueous sodium hydroxide (65 c.c.). The crystalline peroxide which separated was filtered off and addition of methyl alcohol to the chloroform filtrate precipitated a further quantity. The total product (61 g.) was washed well with methyl alcohol and dried over sulphuric acid. Crystallisation from chloroform gave *o-nitrobenzoyl peroxide* in colourless plates, m. p. 147° (explosive decomp.) (Found: C, 51·4; H, 2·3. $C_{14}H_8O_8N_2$ requires C, 50·6; H, 2·4%).

The following peroxides were similarly prepared: *m*-nitrobenzoyl (m. p. 134°), *p*-nitrobenzoyl (m. p. 157°), *p*-chlorobenzoyl (m. p. 138°), *p*-methoxybenzoyl (m. p. 127° from alcohol; purity 97·8% by titration), 1-naphthoyl * (m. p. 98°), 2-naphthoyl * (m. p. 140° from chloroform) (Found: C, 77·1; H, 4·1. Calc. for $C_{22}H_{14}O_4$: C, 77·2; H, 4·1%), 2 : 2′-*dicarbomethoxybenzoyl* (Found: C, 60·4; H, 4·1. $C_{18}H_{14}O_8$ requires C, 60·3; H, 3·9%. Purity 99·8% by titration), cinnamoyl peroxide (m. p. 130°), and phenylacetyl. *m*-Nitrobenzoyl peroxide was also prepared by the nitration of benzoyl peroxide as described by Gelissen and Hermans (*Ber.*, 1925, **58**, 293).

2 : 2′-Dicarboxybenzoyl peroxide was prepared from phthalic anhydride by the method of Baeyer and Villiger (*Ber.*, 1901, **34**, 764). Phthaloyl peroxide was prepared from *s-o*-phthaloyl chloride (5 g.), prepared by the method of Ott (*Org. Synth.*, 1931, **11**, 88), which was added with vigorous stirring to a solution of sodium phosphate (10 g.) in 20-vol. hydrogen peroxide (40 c.c.). After ½ hour, 10% aqueous sodium hydroxide (10 c.c.) was added and stirring was continued for 2½ hours. The white precipitate was collected, washed with water, and dried (1 g.; yield 24%). The product decomposed without melting at about 125°. In another preparation a solution of phthaloyl chloride (15 g.) in chloroform (15 c.c.) was shaken with a mixture of 20 vol. hydrogen peroxide (48 c.c.) and 25% aqueous sodium hydroxide (24 c.c.). The precipitated peroxide was collected at the pump, washed with water, and

* Since this work was completed both 1-naphthoyl peroxide and 2-naphthoyl peroxide have been described by Kharasch and Dannley (*J. Org. Chem.*, 1945, **10**, 406), who reported m. p.s of 98·2° and 138° respectively.

dried (4·3 g.; yield 33%). The product decomposed at 125° (cf. von Pechmann and Vanino, *Ber.*, 1894, **27**, 1512).

Phenylacetyl peroxide was prepared by shaking a solution of phenylacetyl chloride (5 g.) in light petroleum (30 c.c.) with a cold mixture of 20-vol. hydrogen peroxide (10 c.c.) and 25% sodium hydroxide (5 c.c.). The peroxide separated in colourless flakes, which were filtered off and washed successively with ice-cold water, methyl alcohol (10 c.c.), and light petroleum (30 c.c.). The dry crystalline peroxide (1 g.) exploded on contact with a spatula. Vanino and Thiele (*Ber.*, 1896, **29**, 1727) recorded m. p. 41° (decomp.) for phenylacetyl peroxide.

Reactions with Benzene.—(i) *o*-Nitrobenzoyl peroxide (5 g.) was added to benzene (45 c.c.) and the mixture boiled under reflux for 18 hours. After removal of excess of benzene by distillation, the residue was heated with 25% aqueous sodium hydroxide (40 c.c.) for 4 hours at 100°. The mixture was extracted with benzene, and on distillation 2-nitrodiphenyl (1·8 g.) was obtained, m. p. and mixed m. p. with an authentic specimen, after crystallisation from dilute alcohol, 37°.

(ii) *m*-Nitrobenzoyl peroxide (25 g.) was refluxed with benzene (100 c.c.) for 24 hours and the product was worked up as described above for the *ortho* compound. After removal of excess of benzene from the extract, a residue of straw-coloured crystals (12 g.) was obtained, which after recrystallisation from alcohol melted, both alone and in admixture with 3-nitrodiphenyl, at 61°.

(iii) *p*-Nitrobenzoyl peroxide (5 g.) was refluxed with benzene (35 c.c.) for 48 hours and the product worked up as for the *ortho* compound. After treatment with alkali the crude 4-nitrodiphenyl was filtered off from the diluted mixture. Crystallisation from alcohol with charcoal gave 4-nitrodiphenyl (1·6 g.), m. p. and mixed m. p. with an authentic specimen, 112°.

(iv) *p*-Methoxybenzoyl peroxide (10 g.) was boiled under reflux with benzene (100 c.c.) for 16 hours. After removal of excess of benzene, the residue was boiled with 10% aqueous-alcoholic sodium hydroxide for 2 hours. The alcohol was removed by distillation and the residue diluted and filtered. The residual solid was distilled in a vacuum and the product (1·4 g.), after crystallisation from alcohol, gave 4-methoxydiphenyl, m. p. 89°.

(v) 2-Naphthoyl peroxide (10 g.) was boiled under reflux with benzene (100 c.c.) for 24 hours. Excess of benzene was removed, and the product was boiled with 10% aqueous-alcoholic sodium hydroxide for 3 hours. The alcohol was distilled off and the residue diluted and filtered. The precipitated solid was collected, washed with hot water, and dried (3·5 g.). The product, purified by distillation with steam followed by crystallisation from alcohol, was 2-phenylnaphthalene, m. p. and mixed m. p. with an authentic specimen, 101°.

(vi) 2 : 2′-Dicarboxybenzoyl peroxide (17 g.) was boiled under reflux with benzene (100 c.c.) for 120 hours; at the end of this time much undissolved material remained which was filtered off (12 g.) and found to consist of substantially pure unreacted peroxide. Concentration of the filtrate deposited a crystalline solid (2 g.), which was recrystallised from benzene. On sublimation, phthalic anhydride was obtained. No other product was isolated. In view of its stability at the temperature of boiling benzene the peroxide (18 g.) was added to nitrobenzene (80 c.c.) stirred at 140°. Carbon dioxide was evolved, and the reaction was completed by heating at 160° for ½ hour. After removal of excess of nitrobenzene under reduced pressure, the residue was dissolved in benzene and extracted with aqueous sodium hydroxide (5%). Acidification followed by extraction with ether gave a mixture of acids (17·5 g.) which was refluxed with chloroform (150 c.c.), and the insoluble phthalic acid (7·6 g.) filtered off. Concentration of the chloroform solution to 30 c.c. resulted in the separation of 4-nitrodiphenyl-2′-carboxylic acid (2·3 g.), m. p. and mixed m. p. 224—226° (cf. Grieve and Hey, *J.*, 1932, 1891, footnote). Evaporation of the filtrate left a viscous solid, from which 2-nitrodiphenyl-2′-carboxylic acid (1·7 g.), m. p. and mixed m. p. 165—166°, was isolated by crystallisation from benzene (cf. Bell, *J.*, 1934, 838).

(vii) 2 : 2′-Dicarbomethoxybenzoyl peroxide (15 g.) was boiled under reflux with benzene (100 c.c.) for 24 hours. No unchanged peroxide could be detected at the end of this period. The solution was extracted with 10% aqueous sodium carbonate (3 × 50 c.c.), and the benzene was then evaporated and the residue distilled. Methyl diphenyl-2-carboxylate (4·4 g.) was collected at 300—310°. A portion of this product (2 g.) was hydrolysed with 10% alcoholic potassium hydroxide (25 c.c.) to give diphenyl-2-carboxylic acid, m. p. and mixed m. p. 112° after crystallisation from dilute alcohol. A portion of the acid (0·5 g.), dissolved in concentrated sulphuric acid (5 c.c.), gave a deep red coloration and, on dilution and addition of alkali, fluorenone (0·4 g.) was precipitated, m. p. and mixed m. p. 83° after crystallisation from alcohol.

(viii) The peroxide derived from 1-methyl hydrogen 4-nitrophthalate was obtained as follows: finely powdered 4-nitrophthalic anhydride was boiled under reflux for ½ hour with methyl alcohol (cf. Wegscheider and Lipschitz, *loc. cit.*), and after removal of the excess of methyl alcohol the residual syrup crystallised. The resulting 1-methyl ester of 4-nitrophthalic acid was converted into the acid chloride by reaction with thionyl chloride at 60°. The crude acid chloride (55 g.) in the form of a viscous syrup was dissolved in chloroform (50 c.c.) and shaken with a mixture of 20-vol. hydrogen peroxide (80 c.c.) and 25% aqueous sodium hydroxide (40 c.c.). The solid which separated together with the chloroform layer was treated with methyl alcohol, and the oil which separated solidified overnight at 0° (25·4 g.; yield 50%). The product was dissolved in hot acetone (200 c.c.), and addition of cold methyl alcohol (350 c.c.) precipitated a pale yellow solid (A) (10 g.), m. p. 143°. Water was added to the filtrate until it became opalescent, and on standing colourless prisms separated (B) (12·5 g.), m. p. 110°. These two products were treated separately as follows.

Peroxide (*A*). The *peroxide* was further purified by reprecipitation several times from acetone by addition of methyl alcohol. The final product had m. p. 153° (Found: C, 48·4; H, 2·85. $C_{18}H_{12}O_{12}N_2$ requires C, 48·2; H, 2·7%. Purity by titration 100·1%). The peroxide (7·5 g.) was boiled under reflux with benzene (100 c.c.) for 48 hours, at the end of which time no unreacted peroxide could be detected. On cooling, straw-coloured needles separated (2 g.), m. p. 139°, which after recrystallisation from benzene was raised to 143°, which agrees with the recorded m. p. for 2-methyl hydrogen 4-nitrophthalate (cf. Wegscheider and Kuśy von Dúbrav, *Monatsh.*, 1903, **24**, 825). The filtrate was extracted with 10% aqueous sodium carbonate, and the aqueous layer acidified and extracted with ether.

Evaporation of the ether gave a further quantity of crude 2-methyl hydrogen 4-nitrophthalate (1·8 g.), m. p. 137°. The benzene solution was evaporated and the residue distilled in high vacuum. A fraction (2·7 g.) collected at 70—80°/0·00001 mm. solidified on cooling. *Methyl 4-nitrodiphenyl-2-carboxylate* separated in needles m. p. 70° after crystallisation from dilute alcohol (Found: C, 65·6; H, 4·5. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3%). A portion of this ester (0·6 g.) was hydrolysed by heating with 10% alcoholic potassium hydroxide (10 c.c.). The solution was diluted to 100 c.c. with water and acidified. The precipitated 4-nitrodiphenyl-2-carboxylic acid (0·5 g., m. p. 170°) separated from dilute alcohol in needles, m. p. 172° (cf. Heilbron, Hey, and Wilkinson, *J.*, 1938, 115). A portion of the purified acid (0·4 g.) was dissolved in concentrated sulphuric acid (5 c.c.) and the solution poured into cold water (20 c.c.) and made slightly alkaline. The precipitated 2-nitrofluorenone crystallised from alcohol in golden needles, m. p. and mixed m. p. 218°.

Peroxide (*B*). The *peroxide* (8·1 g.), after purification by precipitation (Found: C, 49·1; H, 2·8. $C_{18}H_{12}O_{12}N_2$ requires C, 48·2; H, 2·7%), was boiled under reflux with benzene (100 c.c.) and the product worked up as described above for peroxide (A). The acid (4·5 g.) liberated on acidification of the carbonate extracts proved to be 4-nitrophthalic acid, m. p. and mixed m. p. 163°. The viscous residue obtained on evaporation of the benzene was hydrolysed with alcoholic potassium hydroxide, and after dilution and acidification a crude acid (2 g.) was obtained which was distilled at 200—220°/0·00001 mm. The resulting orange-coloured crystalline product (0·3 g.), m. p. 160—172° after crystallisation from dilute acetic acid, was treated with concentrated sulphuric acid to effect ring closure. The product was poured into water, and the mixture made slightly alkaline and filtered. Crystallisation from alcohol gave yellow-brown plates and golden needles (m. p. *ca.* 190°). Recrystallisation from glacial acetic acid gave a small quantity of 2-nitrofluorenone m. p. 214°. A second product, m. p. 220—225°, regarded as 3-nitrofluorenone from melting point, colour, and crystalline form, could not be obtained pure.

(ix) Phenylacetyl peroxide was prepared in benzene solution by shaking a solution of phenylacetyl chloride (10 g.) in benzene (50 c.c.) with 20-vol. hydrogen peroxide (20 c.c.) and aqueous 25% sodium hydroxide (10 c.c.) at 10° for 20 minutes. The benzene layer was separated, dried over sodium sulphate at 10°, and after decantation allowed to warm up to 30°. When evolution of gas had ceased, excess of benzene was removed by distillation and the residue was boiled under reflux with 10% aqueous alcoholic sodium hydroxide (30 c.c.). The alcohol was distilled off, and the solution diluted to 100 c.c. and extracted with ether. Distillation of the extract gave a fraction, b. p. 150—180°/20 mm., which partially solidified on cooling. Crystallisation of the solid from dilute alcohol gave dibenzyl (1·2 g.), m. p. and mixed m. p. 51°.

(x) Cinnamoyl peroxide (20 g.) was boiled under reflux with benzene (500 c.c.) for 24 hours. After removal of most of the excess of benzene the residue was boiled under reflux with 25% aqueous alcoholic sodium hydroxide for 16 hours. The mixture was extracted with benzene; removal of the solvent from the dried extract left a residue which was distilled under reduced pressure. A small quantity of stilbene (0·6 g.) was collected at 160°/20 mm. which solidified on cooling, and had m. p. 124° after crystallisation from alcohol.

Reactions with Pyridine.—(i) Benzoyl peroxide (60 g.) was added in small quantities to pyridine (200 c.c.) stirred at 100°. Considerable evolution of gas ensued, and the rate of addition was adjusted so that no increase in temperature was caused. When the addition was complete, excess of pyridine was removed by distillation and the residue was boiled under reflux for 5 hours with a mixture (250 c.c.) of equal parts by volume of concentrated hydrochloric acid and water. The mixture was subsequently made alkaline with 30% aqueous sodium hydroxide and extracted thrice with benzene (500 c.c.). After removal of benzene the residue was distilled under reduced pressure, and two fractions were collected, b. p. 156—186° (13·5 g.), and b. p. 200—210° (0·6 g.). The two fractions were combined, dissolved in hot alcohol, and added to a hot solution of picric acid (30 g.) in alcohol (390 c.c.). The mixture was boiled under reflux for ½ hour and filtered hot (filtrate, A). The residue (12 g.) was fractionally crystallised from alcohol, and yielded bright golden needles of 4-phenylpyridine picrate (3·8 g.), m. p. and mixed m. p. 196°. The alcoholic filtrate (A) was cooled, and the crystalline mass which separated (47 g.) was fractionally crystallised from alcohol. Repeated crystallisation gave specimens of pure 3-phenylpyridine picrate in fibrous yellow needles, m. p. and mixed m. p. 163°, and 2-phenylpyridine picrate in orange-yellow prisms, m. p. and mixed m. p. 176°. The main bulk of the product from the filtrate consisted of impure 2-phenylpyridine picrate. In another experiment the peroxide (60 g.) was added to pyridine (200 c.c.) as above, and after removal of excess of pyridine at 100° under reduced pressure, the residue was dissolved in benzene (750 c.c.) and extracted first with 5% aqueous sodium hydroxide and subsequently with 15% hydrochloric acid. Acidification of the alkaline extract deposited benzoic acid (36 g.). Basification of the acid extract, followed by extraction with benzene and evaporation, gave a mixture of crude phenylpyridines (19 g.), from which the three isomerides were isolated in the form of their picrates. The original benzene extract left a tarry residue (5·4 g.) on evaporation.

(ii) *o*-Nitrobenzoyl peroxide (20 g.) was added to pyridine (100 c.c.) stirred at 110°. A vigorous reaction ensued. After removal of excess of pyridine by distillation the residue was dissolved in benzene and extracted successively with 5% aqueous sodium hydroxide and with 15% hydrochloric acid. The alkaline washings gave *o*-nitrobenzoic acid (17·3 g.), m. p. and mixed m. p. 146°. The basic fraction consisted of a small tarry residue (1·7 g.), whereas the neutral fraction gave a small quantity (0·5 g.) of an oil with the odour of nitrobenzene. In similar reactions with *m*-nitrobenzoyl peroxide (20 g.) and with *p*-nitrobenzoyl peroxide (20 g.), the main products were *m*-nitrobenzoic acid (18 g.) and *p*-nitrobenzoic acid (11 g.) respectively.

(iii) *p*-Chlorobenzoyl peroxide (20 g.) was added to pyridine (80 c.c.) stirred at 95°. When evolution of gas had ceased the mixture was boiled under reflux for 2 hours and excess of pyridine was removed under reduced pressure. The residue was boiled with 25% aqueous sodium hydroxide (100 c.c.) and extracted with benzene. After removal of solvent, the residue (6 g.) was distilled under reduced pressure and the main fraction (3·4 g.), collected at 170—175°/20 mm., was dissolved in hot alcohol and treated with a hot solution of picric acid (8 g.) in alcohol (50 c.c.). Fractionation of the resulting picrates from acetone gave 4-*p*-chlorophenylpyridine picrate, m. p. and mixed m. p. 228—229°, and 2-*p*-chlorophenylpyridine picrate, m. p. and mixed m. p. 167—168° (cf. Butterworth, Heilbron, and Hey, *J.*, 1940, 356).

(iv) *p*-Methoxybenzoyl peroxide (20 g.) was added to pyridine (80 c.c.) stirred at 100—110°, and the product was worked up as described above for the reaction with *p*-chlorobenzoyl peroxide. The basic product (3·4 g.), b. p. 170—195°/14 mm., which solidified when cold, was treated with alcoholic picric acid; fractionation of the resulting picrates from acetone gave 2-*p*-methoxyphenylpyridine picrate, m. p. and mixed m. p. 190°, and 4-*p*-methoxyphenylpyridine picrate, m. p. and mixed m. p. 205° (cf. Haworth, Heilbron, and Hey, *J.*, 1940, 360).

(v) 1-Naphthoyl peroxide (15 g.) was stirred with pyridine (80 c.c.) at 100°. When reaction had ceased excess of pyridine was removed in a vacuum, and the residue was dissolved in benzene (300 c.c.), which was extracted successively with 5% aqueous sodium hydroxide and 15% hydrochloric acid. Evaporation of the benzene left a small tarry residue (1·4 g.), from which a small quantity of naphthalene sublimed on heating (0·05 g.; m. p. and mixed m. p. 79°). The acid extract was basified and extracted with benzene, evaporation of which left a dark liquid residue (1·9 g.), which was treated with alcoholic picric acid. Crystallisation of the resulting picrate from acetone (with charcoal) gave a *1-naphthylpyridine picrate* in pale yellow needles, m. p. 196° (Found: C, 58·1; H, 3·3; N, 12·8. $C_{15}H_{11}N,C_6H_3O_7N_3$ requires C, 58·1; H, 3·2; N, 12·9%). No isomerides were isolated.

(vi) 2-Naphthoyl peroxide (20 g.) was added to pyridine (80 c.c.), stirred at 105°, and the reaction product was worked up as described in (v). A small quantity of naphthalene, m. p. and mixed m. p. 79°, was isolated from the neutral fraction by sublimation. The basic residue (2·6 g.) was treated with a solution of picric acid (3 g.) in boiling alcohol, and fractional crystallisation of the resulting picrates from acetone (with charcoal) gave three isomeric 2-naphthylpyridine picrates, (*a*) yellow needles, m. p. 200° (Found: C, 58·0; H, 3·2. Calc. for $C_{15}H_{11}N,C_6H_3O_7N_3$: C, 58·1; H, 3·2%); (*b*) yellow needles, m. p. 179° (Found: N, 12·8. Calc. for $C_{15}H_{11}N,C_6H_3O_7N_3$: N, 12·9%); (*c*) yellow prisms, m. p. 216°, in very small yield. The compounds (*a*), (*b*), and (*c*) showed no depression in melting point on admixture with the corresponding compounds prepared from 1-2′-naphthyl-3 : 3-dimethyltriazen and pyridine (Elks and Hey, *J.*, 1943, 444).

(vii) 2 : 2′-Dicarbomethoxybenzoyl peroxide (40 g.) was added to pyridine (150 c.c.) stirred at 100°. When reaction was complete, excess of pyridine was removed under reduced pressure and the residue dissolved in benzene (500 c.c.) and extracted with a saturated aqueous solution of sodium hydrogen carbonate. After removal of the benzene the residue was distilled under reduced pressure, and two fractions were collected: (*a*) b. p. 60°/0·1 mm. (2·3 g.); (*b*) b. p. 110—150°/0·1 mm. (4·2 g.). Fraction (*a*) was identified as methyl benzoate by hydrolysis. Fraction (*b*) was treated with a hot solution of picric acid (6 g.) in alcohol (40 c.c.). Fractional crystallisation of the resulting picrates from acetone gave two isomeric *methyl o-pyridylbenzoate picrates*: (*a*) orange-yellow prisms, m. p. 243° (0·5 g.) (Found: C, 51·2; H, 3·0. $C_{13}H_{11}O_2N,C_6H_3O_7N_3$ requires C, 51·6; H, 3·2%); (*b*) fine yellow matted fibres, m. p. 196° (1·3 g.) (Found: C, 51·9; H, 3·2%).

(viii) Cinnamoyl peroxide (30 g.) was added in small quantities to pyridine (200 c.c.) stirred at 110°. When evolution of gas ceased, excess of pyridine was removed under reduced pressure. The residue was dissolved in benzene (500 c.c.) and extracted first with 10% aqueous sodium hydroxide and then with 10% hydrochloric acid. The acid extract was made alkaline, extracted with benzene, and the benzene removed. The residue (0·7 g.) was treated with a solution of picric acid (1 g.) in boiling alcohol. The resulting picrates were crystallised from alcohol, and α-stilbazole picrate was obtained in golden needles, m. p. and mixed m. p. with an authentic specimen 204°. A portion of the picrate was warmed with 5% aqueous sodium hydroxide and the liberated α-stilbazole was extracted with ether. After the ethereal extract had been washed free from picric acid, the dried solution was evaporated and the residual α-stilbazole isolated, m. p. and mixed m. p. 91°. The authentic specimen was made from α-stilbazole prepared from benzaldehyde and 2-methylpyridine as described by Lénárt (*Annalen*, 1915, **410**, 95).

Miscellaneous Reactions.—m-*Nitrobenzoyl peroxide and benzoic acid.* The peroxide (20 g.) was added to molten benzoic acid (75 g.) at 125°, and when addition was complete the temperature was raised to 150° for 1 hour. The product was dissolved in 10% aqueous sodium hydroxide (500 c.c.) and extracted with ether. The aqueous layer was warmed to remove ether, and concentrated hydrochloric acid was added to the hot solution until precipitation began. Further acidification was then effected with 5% hydrochloric acid (30 c.c.) to give precipitate (A), with a further 20 c.c. to give precipitate (B), and with a further 20 c.c. to give precipitate (C). Precipitate (A) was sublimed in high vacuum (150°/0·00001 mm.), and the sublimate (1·2 g.) crystallised from glacial acetic acid. *3-Nitrodiphenyl-4′-carboxylic acid* separated in yellow plates, m. p. 301° (Found: C, 64·4; H, 3·3. $C_{13}H_9O_4N$ requires C, 64·2; H, 3·7%). In similar manner the sublimate from precipitate (B) (0·9 g.; 120°/0·00001 mm.) was crystallised from glacial acetic acid, and *3-nitrodiphenyl-3′-carboxylic acid* separated in flat needles, m. p. 262° (Found: C, 63·9; H, 4·0%). Precipitate (C) consisted almost exclusively of benzoic acid. Evaporation of the ethereal extract from the alkaline washing left a brown syrup (0·7 g.), from which a small quantity of 3 : 3′-dinitrodiphenyl separated, m. p. 200° after crystallisation from dilute alcohol (cf. Ullmann and Bielecki, *Ber.*, 1901, **34**, 2177).

Benzoyl peroxide and quinoline. Benzoyl peroxide (60 g.) was added to quinoline (200 g.) stirred at 100—105°. When reaction was complete, the temperature was raised to 160° for ½ hour, and excess of quinoline was removed under reduced pressure. The residue was dissolved in benzene (300 c.c.) and extracted with aqueous sodium hydrogen carbonate. The distilled quinoline was also extracted with 5% aqueous sodium hydroxide, and acidification of the combined extracts gave benzoic acid (37 g.). After evaporation of the benzene the residue was distilled and two fractions were collected: (*a*) b. p. 140—200°/0·5 mm. (17·5 g.); (*b*) b. p. 200—250°/0·5 mm. (4·5 g.). Fraction (*a*) was treated with a hot alcoholic solution of picric acid; fractional crystallisation of the resulting picrates from acetone gave 4-phenylquinoline picrate (2·5 g.), m. p. and mixed m. p. 224°, 5-phenylquinoline picrate, m. p. and mixed m. p. 208—210°, and the following picrates which gave mutual melting point depressions both with each other and with authentic specimens of phenylquinoline picrates: (*a*) yellow sphaerolites, m. p. 204° (Found: N, 12·1. $C_{15}H_{11}N,C_6H_3O_7N_3$ requires N, 12·9%); and in very small quantity (*b*) yellow fibrous needles, m. p. 213°, and (*c*) yellow needles, m. p. 192°.

Authentic specimens of the picrates of the seven isomeric phenylquinolines were prepared. 2-Phenyl-

quinoline and 3-phenylquinoline were prepared by the method of Friedländer and Gohring (*Ber.*, 1883, **16**, 1833). The picrates were prepared in the normal manner: that of the former melted at 191° and of the latter at 205° (cf. Knorr, *Annalen*, 1888, **245**, 380; Hübner, *Ber.*, 1908, **41**, 483). 4-Phenylquinoline was prepared by the method of Kenner and Statham (*J.*, 1935, 301) and converted into the picrate, m. p. 225°. 6- and 8-Phenylquinoline were prepared from 4-aminodiphenyl and 2-aminodiphenyl respectively by a modification of the method of La Coste and Sorger (*Annalen*, 1885, **230**, 8). Concentrated sulphuric acid (3·5 c.c.) was added slowly with cooling to a mixture of 4-aminodiphenyl (3·5 g.), anhydrous glycerol (4·5 c.c.), and sodium *m*-nitrobenzenesulphonate (4 g.). The mixture was heated in an oil-bath at 130° under reflux and finally at 150° with frequent shaking. As soon as the reaction started the flask was removed from the oil-bath, and after the vigorous reaction had subsided heating was continued at 160° for 7 hours. The cold reaction mixture was diluted to 300 c.c. and made strongly alkaline with ammonia. The precipitated solid was extracted with boiling benzene; evaporation of the benzene left a residue of 6-phenylquinoline (2·3 g.), m. p. 109° after crystallisation from alcohol. The *picrate* separated from acetone in flat yellow needles, m. p. 205° (Found: N, 12·7. $C_{15}H_{11}N,C_6H_3O_7N_3$ requires N, 12·9%). By using 2-aminodiphenyl in place of 4-aminodiphenyl, 8-phenylquinoline was prepared in 44% yield as an oil, b. p. 210°/20 mm. The *picrate* separated from acetone in yellow needles, m. p. 200° (Found: N, 12·6. $C_{15}H_{11}N,C_6H_3O_7N_3$ requires N, 12·9%). Möhlau and Berger (*Ber.*, 1893, **26**, 2004) have recorded m. p. *ca.* 210° for this picrate, which was prepared from a base derived from the action of solid benzenediazonium chloride on quinoline. A mixture of 5- and 7-phenylquinoline was prepared from the reaction between 3-aminodiphenyl (6 g.), glycerol (8 c.c.), sodium *m*-nitrobenzenesulphonate (6 g.), and concentrated sulphuric acid (6 c.c.), carried out as described above for the reaction with 4-aminodiphenyl. The product (3·7 g.) was treated with alcoholic picric acid, and the picrates were boiled under reflux with alcohol (450 c.c.) and filtered off. Recrystallisation of the insoluble residue from acetone gave *7-phenylquinoline picrate* in stout golden needles, m. p. 210°, which depressed the melting point of 5-phenylquinoline picrate (Found: N, 12·3. $C_{15}H_{11}N,C_6H_3O_7N_3$ requires N, 12·9%). A further quantity of 7-phenylquinoline picrate separated from the mother liquor, and finally a small quantity of 5-phenylquinoline picrate separated, m. p. 210° both alone and on admixture with an authentic specimen prepared by the action of 1-5′-quinolyl-3 : 3-dimethyltriazen on benzene (Elks and Hey, *loc. cit.*).

Benzoyl peroxide and 2 : 2 : 4-trimethylpentane. The peroxide (54 g.) was added to 2 : 2 : 4-trimethylpentane (200 c.c.) stirred at 100°. When reaction had ceased, excess of trimethylpentane was removed by distillation, and the residue was dissolved in ether (200 c.c.) and extracted with aqueous sodium hydrogen carbonate. Acidification of the aqueous extracts deposited benzoic acid (14 g.). Fractional distillation of the recovered trimethylpentane gave a fraction (10 c.c.), boiling below 84°, which was identified as benzene by conversion into *m*-dinitrobenzene. After removal of the ether, the residue was distilled under reduced pressure and the following fractions were collected: (*a*) b. p. 113—126°/12 mm. (6·5 g.); (*b*) b. p. 142—160°/12 mm. (2·8 g.); (*c*) b. p. 150—220°/0·2 mm. (5·2 g.); (*d*) b. p. 150—250°/0·00001 mm. (3·0 g.). Fraction (*a*) deposited crystals of diphenyl, m. p. and mixed m. p. 70°. Fraction (*b*) gave a further quantity of benzoic acid, and fraction (*c*) gave diphenyl-4-carboxylic acid, m. p. and mixed m. p. 220—222°. Fraction (*d*) was a resin.

The authors thank Imperial Chemical Industries (Dyestuffs Group) Limited for grants and gifts of chemicals.

Imperial College of Science and Technology,
(University of London), London, S.W.7.
King's College,
(University of London), Strand, London, W.C.2. [*Received, February 16th*, 1948.]

---

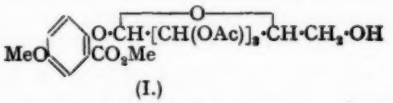
451. *Syntheses of Glycosides. Part XIII. Primulaverin.*

By D. N. Chaudhury, H. I. King, and Alexander Robertson.

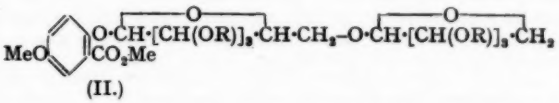
A synthesis of the β-primeveroside of methyl 5-methoxysalicylate is described and evidence has been obtained in support of the view that the mixture originally named primulaverin by Goris and his co-workers (*loc. cit.*) is a mixture of the foregoing glycoside and primeverin.

Along with primeverin (Part X, *J.*, 1933, 1618) Goris and his co-workers (*Bull. Sci. pharmacol.*, 1909, **16**, 695; 1912, **19**, 577; 1920, **27**, 13) isolated glycosidic material, m. p. 163°, which at first they considered to be an individual substance, primulaverin, but which they subsequently concluded was a mixture of the primeverosides of methyl 4-methoxysalicylate (primeverin) and 5-methoxysalicylate since on hydrolysis the purest specimens obtained invariably gave rise to mixtures of 4- and 5-methoxysalicylic acid. Further, these authors also suggested that the product, m. p. 163°, probably arose from the crystallisation of two isomorphous substances which attain a very stable equilibrium, causing their separation to be difficult, a view which seemed reasonable since the two glycosides are very similar in constitution. Though Goris continued to call the (mixed) material, m. p. 163°, by the name primulaverin, we propose to reserve this name for the β-primeveroside of methyl 5-methoxysalicylate (II, R = H), a synthesis of which was clearly an essential preliminary step in the clarification of this problem.

In the first instance two of us (H. I. K. and A. R.) in 1935 attempted the synthesis of the required primeveroside by the route adopted in the case of monotropitoside (gaultherin) (Part VIII, *J.*, 1931, 1881) and of primeverin (Part X, *J.*, 1933, 1618), a general procedure which was originally devised in order to avoid the troublesome preparation of acetylated biosidyl bromides, *e.g.*, from primeverose. Accordingly, the condensation of methyl 5-methoxysalicylate and *O*-tetra-acetyl-α-glucosidyl bromide by the quinoline–silver oxide method gave rise to *methyl* 2-O-*tetra-acetyl*-β-*glucosidoxy*-5-*methoxybenzoate* in good yield, which on deacetylation furnished *methyl* 2-β-*glucosidoxy*-5-*methoxybenzoate*. On acetylation the *trityl* ether of the latter compound yielded *methyl* 2-(2′ : 3′ : 4′-O-*triacetyl*-6′-O-*trityl*-β-*glucosidoxy*)-5-*methoxybenzoate* which on removal of the trityl group in the usual manner gave rise to the *triacetate* (I)



(I.)



(II.)

but since attempts to induce this substance to react with *O*-triacetyl-α-xylosidyl bromide so as to give the hexa-acetate of primulaverin (II, R = Ac) failed, we abandoned this route. Subsequently, Mauthner (*J. pr. Chem.*, 1940, **156**, 150) described the synthesis of the *O*-hexa-acetyl-β-primeveroside of methyl 5-methoxysalicylate, m. p. 198—199°, with the aid of Zemplen's *O*-hexa-acetyl-α-primeverosidyl bromide (*Ber.*, 1939, **72**, 49) but does not appear to have deacetylated the product. Accordingly, we have repeated the preparation of the hexa-acetate of primulaverin (II, R = Ac) which we found to have m. p. 212—214°. Deacetylation of this substance by the methyl-alcoholic ammonia process gave primulaverin (II, R = H) as a *penta-hydrate*, m. p. 195—197°, which appears to be difficult to dehydrate but which on acetylation re-formed the original hexa-acetate, m. p. and mixed m. p. 212—214°.

Having obtained primulaverin, we attempted to prepare Goris's product by recrystallising a mixture of synthetical specimens of primulaverin and primeverin from methanol; the latter compound, m. p. 205°, was obtained by repeating the synthesis of Jones and Robertson (Part X, *loc. cit.*). The solid (A), which separated, had m. p. 198—200° changing to 202° on crystallisation from the same solvent, and was apparently almost pure primeverin. Concentration of the mother-liquor from (A) gave a product which had m. p. 170—172°, unchanged on repeated recrystallisation, and appeared to be predominantly primulaverin contaminated with primeverin. In this connection it is of interest to note that the natural mixture kindly supplied to us by Professor Goris was found to have m. p. 167—169°. We then determined the melting point curve for the mixture of synthetical glycosides and found that the minimum point on the curve, which corresponds to the melting point of Professor Goris's specimen, was given by a mixture containing approximately 75% of primulaverin pentahydrate and 25% of primeverin. Thus it would appear that the evidence obtained so far serves to substantiate the suggestion made by Goris and his co-workers that the product originally named primulaverin by them is a mixture of two glycosides, but final confirmation of this must await the isolation of a substantial supply of the natural mixture to enable us to undertake the separation of the components.

Experimental.

5-Hydroxysalicylic Acid.—The following procedure for the preparation of this acid was found to be superior to those given in the literature. Sodium nitrite (29 g.), dissolved in water (100 ml.), was gradually added to a vigorously stirred mixture of aniline (36 g.), concentrated hydrochloric acid (63 ml.; *d* 1·9), and crushed ice (300 g.), and 15 minutes later a solution of salicylic acid (53·5 g.) and sodium carbonate (200 g. of hydrate) in water (1000 ml.) was introduced. The resulting azo-derivative of salicylic acid was collected, washed with water, and gradually added to a well-stirred solution of stannous chloride (172 g.) in concentrated hydrochloric acid (350 ml.) and the mixture heated on the steam-bath until a clear solution was obtained, which was then rapidly filtered through a glass-wool filter pad. After the addition of concentrated hydrochloric acid (500 ml.), the filtrate deposited in the course of 24 hours a mass of colourless prisms, and these were collected, washed with dilute hydrochloric acid (500 ml.), and recrystallised from hot water (500 ml.). The resulting 5-aminosalicylic acid was mixed with ice (300 g.) and concentrated hydrochloric acid (70 ml.) and then converted into the corresponding diazonium salt by the addition of 30% aqueous sodium nitrite (100 ml.). This product, which formed almost colourless needles, giving a red-violet ferric reaction in alcohol, was collected and washed with a little water at 0°. The moist diazonium chloride (from 53 g. of salicylic acid) was heated with 50% sulphuric acid (200 ml.) until the vigorous evolution of nitrogen had ceased (1 hour), and on being kept at room temperature the resulting solution gradually deposited 5-hydroxysalicylic acid, m. p. 200°, after recrystallisation from dilute hydrochloric acid (yield, 15 g.).

A solution of sodium hydroxide (6 g.) in water (60 ml.) was added gradually during 20 minutes to a vigorously agitated mixture of 5-hydroxysalicylic acid (12 g.) and methyl sulphate (15 ml.), and

then after the addition of more hydroxide (4 g.) in water (40 ml.) the reaction mixture was heated on the steam-bath for ½ hour, cooled, and acidified with sulphuric acid. 5-Methoxysalicylic acid was isolated from the crude product by extraction with boiling water (charcoal) and obtained in almost colourless needles, m. p. 144°, after recrystallisation, having a deep blue ferric reaction (compare Graebe and Martz, *Annalen*, 1905, **340**, 213) (yield, 12 g.). Esterification of the acid with boiling methanol and sulphuric acid for 10 hours gave the methyl ester, b. p. 143—144°/16 mm.

Methyl 2-O-Tetra-acetyl-β-glucosidoxy-5-methoxybenzoate.—To ensure success in this experiment it is essential that all the reactants should be pure and dry.

To a paste of methyl 5-methoxysalicylate (5 g.), *O*-tetra-acetyl-α-glucosidyl bromide (15 g.), and quinoline (6 ml.), " active " silver oxide (7 g.) was added with stirring which was continued for 15—20 minutes; the mixture was occasionally cooled by immersion in tap water. The reaction mixture was then kept in a desiccator over soda–lime for ½ hour, stirred for 10 minutes, and 3 hours later extracted with warm acetic acid (50 ml.), and the filtered extract was poured into water (500 ml.). Next day the *product* was collected, washed with water, and crystallised from a small volume of methyl alcohol, forming colourless rods (7·3 g.), m. p. 117°, $[\alpha]_D^{20°}$ −43·95° (in acetone) (Found: C, 54·0; H, 5·5. $C_{23}H_{28}O_{13}$ requires C, 53·9; H, 5·5%). The compound is soluble in alcohol, ethyl acetate, and benzene, and insoluble in light petroleum.

Methyl 2-β-Glucosidoxy-5-methoxybenzoate.—Methyl alcohol containing the foregoing acetate (8 g.) in suspension was saturated with ammonia at 0°, and the resulting solution kept at 0° for 6 hours. Removal of the ammonia and the solvent in a vacuum at room temperature left an oil which gradually solidified and was then extracted with methanol. Crystallisation of the residue from ethyl acetate–methanol gave the glucoside as a *hemihydrate* (3·5 g.), m. p. 170° after sintering at 115°, soluble in water and alcohol, $[\alpha]_D^{20°}$ −50·63° (in water) (Found: C, 51·1; H, 6·1. $C_{15}H_{20}O_9,0{\cdot}5H_2O$ requires C, 51·0; H, 6·0%).

Methyl 2-(2′ : 3′ : 4′-O-Triacetyl-β-glucosidoxy)-5-methoxybenzoate.—A mixture of the foregoing glucoside (3·9 g., dried in a high vacuum at 90° for 1 hour and then at 100° for 3 hours), trityl chloride (3 g.), and pyridine (25 ml.) was heated on the steam-bath for 1 hour and was treated next day with acetic anhydride (25 ml.). Three days later the mixture was poured into water (400 ml.), and the solid collected, well washed with water, and crystallised from methyl alcohol (charcoal), giving the 2-2′ : 3′ : 4′-O-*triacetyl*-6′-O-*trityl*-β-*glucoside* of methyl 5-methoxysalicylate in colourless rods (6 g.), m. p. 141°, $[\alpha]_D^{20°}$ −31·5° (in acetone) (Found: C, 67·0; H, 5·8. $C_{40}H_{40}O_{12}$ requires C, 67·3; H, 5·6%). Scission of this trityl ether (1 g.), dissolved in acetic acid (4 ml.), was effected with a saturated solution of hydrogen bromide in acetic acid (0·5 ml.) in the course of 1 minute, and the rapidly filtered mixture immediately poured into ice-water (100 ml.). A solution of the gummy precipitate in chloroform (150 c.c.) was washed several times with ice-water, dried over calcium chloride, and evaporated in a vacuum at 30°. Crystallisation of the residue from ethyl acetate–light petroleum (b. p. 40—60°) gave the 2-2′ : 3′ : 4′-O-*triacetyl*-β-*glucoside* of methyl 5-methoxysalicylate as a *hemihydrate* in tiny colourless prisms (0·6 g.), m. p. 160°, $[\alpha]_D^{20°}$ −54·93° (in acetone), soluble in benzene, alcohol, and chloroform (Found, in material dried in air: C, 52·7; H, 5·6. $C_{21}H_{26}O_{17},0{\cdot}5H_2O$ requires C, 52·6; H, 5·6%. Found, in material dried in a high vacuum at 90°: C, 53·3; H, 5·4. $C_{21}H_{26}O_{12}$ requires C, 53·6; H, 5·5%).

O-*Hexa-acetyl-β-primeveroside of Methyl 5-Methoxysalicylate* (II, R = Ac).—" Active " silver oxide (5 g.) was gradually added with stirring to a paste of methyl 5-methoxysalicylate (1·8 g.), *O*-hexa-acetyl-α-primeverosidyl bromide (Zemplen, *Ber.*, 1939, **72**, 49) (6·4 g.), and anhydrous quinoline (10 ml.), and the mixture stirred for 20 minutes. Next day the product was extracted with warm acetic acid (80 ml.), the filtered extract (charcoal) diluted with water (400 ml.), and the precipitate crystallised from methyl alcohol, giving the hexa-acetate (4·5 g.) in rectangular prisms, m. p. 212—214°, $[\alpha]_D^{20°}$ −31·2° (*c*, in chloroform, 1·28) (Found: C, 52·5; H, 5·7. Calc. for $C_{32}H_{40}O_{19}$: C, 52·7; H, 5·5%) (compare Mauthner, *loc. cit.*, who gives m. p. 198—199°).

β-Primeveroside of Methyl 5-Methoxysalicylate (II, R = H).—Methyl alcohol (200 ml.), containing the foregoing hexa-acetate (2·5 g.), was saturated with ammonia at 0° and 6 hours later the clear solution was evaporated in a vacuum at room temperature. Slow evaporation of a solution of the residual syrup in methyl alcohol (10 ml.) in the course of several days gave the crystalline primeveroside, which was collected, washed with a little ice-cold methyl alcohol, and dissolved in the minimum amount of warm water. This solution was diluted with four times its volume of alcohol and in the course of a week deposited the *pentahydrate* of the glycoside in colourless slender needles, m. p. 195—197°, unchanged after repeated purification, $[\alpha]_D^{20°}$ −20·0° (*c* in water, 0·8) (Found: C, 42·6; H, 6·5. $C_{20}H_{28}O_{13},5H_2O$ requires C, 42·4; H, 6·5%).

Acetylation of the synthetical pentahydrate with acetic anhydride and sodium acetate on the steam-bath for 2 hours regenerated the hexa-acetate, m. p. 212—214°, identical in every way with the original material. Under the same conditions acetylation of a small specimen of natural mixed glycosides supplied by Professor Goris gave rise to a product which formed needles, m. p. 178—180°, from methyl alcohol. A mixture of the two acetates melted at 176—178°.

UNIVERSITY OF LIVERPOOL.

[*Received, January 22nd,* 1948.]

452. *The Chemistry of the Melanins. Part I. The Synthesis of 5 : 6-Dihydroxyindole and Related Compounds.*

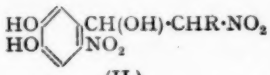
By R. J. S. Beer, Kenneth Clarke, H. G. Khorana, and Alexander Robertson.

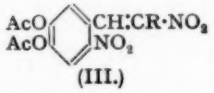
As part of a comprehensive investigation of the chemistry of the melanins the synthesis of 5 : 6-dihydroxyindole and its monomethyl ethers, and of 5 : 6-dihydroxy-2-methylindole, has been carried out. 5 : 6-Dihydroxyindole and its 2-methyl derivative readily undergo oxidative polymerisation yielding melanins.

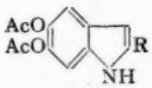
From a survey of the literature on the constitution and mechanism of formation of the natural and synthetic melanins carried out before the initiation of experimental work now in progress on this subject in these laboratories, it became clear that 5 : 6-*dihydroxyindole* is of considerable interest as the unstable intermediate postulated by Raper (*Biochem. J.*, 1927, **21**, 89) in the tyrosinase-catalysed oxidation of tyrosine to melanin. In this reaction the presence of the indole was inferred from the fact that its dimethyl ether (Oxford and Raper, *J.*, 1927, 417) was isolated after a methylation process. The same dihydroxyindole was considered to be formed by the oxidative action of silver oxide on hydroxytyrosine (Raper, *Biochem. J.*, 1930, **24**, 239) whilst under the same conditions methyl-2-3′ : 4′-dihydroxyphenylethylamine gave 5 : 6-dihydroxy-1-methylindole. Burton (*J.*, 1932, 546) attempted to isolate the latter compound from the oxidation mixture, but was unable to obtain crystalline material, nor was the acetate of his product crystalline (compare Bergel and Morrison, *J.*, 1943, 48).

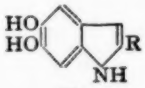
A study of the oxidation of authentic 5 : 6-dihydroxyindole and of related compounds would be expected to throw light on the formation and structure of melanin, but hitherto workers have been restricted to the use of solutions of unknown concentration, containing considerable amounts of other substances. As a preliminary step in our investigations in this field we have therefore extended the method for the synthesis of hydroxyindoles recently developed in these laboratories (*J.*, 1948, 1605) to the preparation of 5 : 6-dihydroxyindole and of certain related indoles (compare *Nature*, 1948, **161**, 525).

(I.)


(II.)


(III.)


(IV.)


(V.)

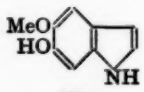
According to Harley-Mason (*Nature*, 1947, **159**, 338), nitroprotocatechuic aldehyde (I), the required starting material for the synthesis of (V, R = H), is not satisfactorily prepared by the demethylenation of 2-nitropiperonylidene diacetate with a mixture of acetic anhydride and nitric acid as described by Parijs (*Rec. Trav. chim.*, 1930, **49**, 36). We found, however, that reasonably good yields * of the required nitro-aldehyde (I) could be obtained under certain carefully standardised conditions (see p. 2224). The condensation of the aldehyde (I) and nitromethane was effected by means of alcoholic potash at 0° and, as in our previous work (*loc. cit.*), the resulting alcohol (II, R = H) was not purified but was converted directly into the *diacetoxystyrene* (III, R = H) in very satisfactory yield by treatment with hot acetic anhydride and sodium acetate. Reduction of (III, R = H) with iron filings and acetic acid afforded the *diacetoxyindole* (IV, R = H; 60%). Since this substance underwent very rapid oxidation in the presence of dilute aqueous alkalis, it seemed likely that the methanolic ammonia deacetylation process used in the synthesis of the much more stable monohydroxyindoles (*loc. cit.*) would fail unless oxygen could be rigorously excluded, and on this account we preferred to attempt the hydrolysis with aqueous-methanolic sodium hydroxide in the presence of a mild reducing agent, sodium hydrosulphite (dithionite). This process furnished a moderate yield of crystalline 5 : 6-dihydroxyindole (V, R = H), which gives a positive Ehrlich and nitroprusside test, forms a red picrate, and shows the expected sensitivity to oxygen in faintly alkaline solution, *e.g.*, in

* Probably owing to an error in transcription the yield given in Parijs's communication (*loc. cit.*) exceeds that theoretically possible, *viz.*, 2·50 g. of nitroprotocatechuic aldehyde from 4·0 g. of nitropiperonylidene diacetate, the theoretical yield being 2·46 g.

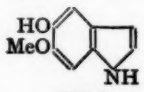
aqueous sodium hydrogen carbonate and to a less extent in neutral aqueous solution (tap water). Solutions of the compound in dilute acetic acid and in non-aqueous solvents are reasonably stable, whilst the solid indole is surprisingly inert. Direct treatment of the alkaline deacetylation mixture with methyl sulphate yielded a crystalline ether, the properties and analysis of which are in agreement with those reported for 5 : 6-dimethoxyindole by Oxford and Raper (*loc. cit.*).

When nitromethane was replaced by nitroethane the same synthetic procedure, with minor modifications, afforded β : 2-*dinitro*-4 : 5-*diacetoxy*-β-*methylstyrene* (III, R = Me) which was converted into 5 : 6-*diacetoxy*-2-*methylindole* (IV, R = Me) and then into 5 : 6-*dihydroxy*-2-*methylindole* (V, R = Me). In this case the initial condensation was less satisfactory and considerable amounts of unchanged nitro-aldehyde were recovered. The dihydroxy-2-methylindole, like 5 : 6-dihydroxyindole, is markedly unstable in faintly alkaline aqueous solution, yielding a dark melanin-like product.

The two monomethyl ethers of 5 : 6-dihydroxyindole, (VI) and (VII), have also been synthesised by the same general method. Thus 6-*acetoxy*-5-*methoxyindole* was obtained from 2-nitro-4-hydroxy-5-methoxybenzaldehyde by way of β : 2-*dinitro*-4-*acetoxy*-5-*methoxystyrene*, and on deacetylation furnished 6-*hydroxy*-5-*methoxyindole* (VI), whilst from 2-nitro-5-hydroxy-4-methoxybenzaldehyde, 5-*hydroxy*-6-*methoxyindole* (VII) was prepared by way of β : 2-*dinitro*-5-*acetoxy*-4-*methoxystyrene* and of 5-*acetoxy*-6-*methoxyindole*.



(VI.)



(VII.)

The deacetylation of the two acetoxy-indoles was effected both by treatment with methanolic ammonia and by the aqueous sodium hydroxide–hydrosulphite method, the latter procedure being definitely superior with 6-hydroxy-5-methoxyindole. Of the two monomethyl ethers, 5-hydroxy-6-methoxyindole is fairly stable in faintly alkaline aqueous solution, whilst the isomeric 6-hydroxy-5-methoxyindole is relatively unstable, but even the latter compound does not undergo oxidative polymerisation with the speed exhibited by 5 : 6-dihydroxyindole or its 2-methyl derivative. Quantitative studies of the latter reaction will be undertaken later, but from our qualitative experiments it appears that the properties of 5 : 6-dihydroxyindole lend support to Raper's view (*loc. cit.*) that this compound is an intermediate in the formation of melanin from tyrosine by enzymatic oxidation.

Experimental.

2-*Nitro*-4 : 5-*dihydroxybenzaldehyde* (2-*Nitroprotocatechuic Aldehyde*) (I).—2-Nitropiperonylidene diacetate (Parijs, *loc. cit.*) (4 g.) was added in small portions during 15 minutes to a mixture of acetic anhydride (20 ml.) and fuming nitric acid (20 ml.; *d* 1·50) which was kept at −12° to −15° and continually agitated. The resulting clear orange-red solution was slowly poured on crushed ice (800 g.) and after the temperature of the mixture had risen to 14° the pale yellow precipitate was collected. When this slightly sticky mass was washed with cold water * (*ca.* 10 ml.), transferred to a round-bottomed flask, and kept for a few minutes, a small quantity of a light orange liquid, containing nitric acid, separated. After this liquor had been decanted the product was heated on the steam-bath with 5% sulphuric acid (15 ml.) for 1 hour, and the resulting hot solution treated with charcoal and filtered. On being kept the cooled filtrate gradually deposited 2-nitro-4 : 5-dihydroxybenzaldehyde as a mass of pale orange, stout rectangular prisms, m. p. 203° (decomp.) (preheated bath). From 4 g. of nitropiperonylidene diacetate the yield of nitroaldehyde varied between 1·25 g. and 1·55 g. and a further quantity of the compound (*ca.* 0·3 g.) was obtained by extraction of the mother-liquor with ether.

β : 2-*Dinitro*-4 : 5-*diacetoxystyrene* (III, R = H).—When potassium hydroxide (1·4 g.), dissolved in water (2 ml.) and 95% alcohol (20 ml.) at 0°, was added dropwise during ½ hour to a manually agitated solution of 2-nitro-4 : 5-dihydroxybenzaldehyde (2 g.) and nitromethane (1·2 g.) in 95% alcohol (20 ml.) maintained at 0° a red precipitate separated. This product became somewhat sticky towards the end of the reaction but on being triturated was converted into a granular powder. After having been kept at 0° for 16 hours the reaction mixture was diluted with ice-water, acidified with dilute hydrochloric acid at 0°, and extracted several times with ether. The combined ethereal extracts were washed three times with aqueous sodium hydrogen sulphite to remove unchanged aldehyde, dried, and evaporated, leaving a product which on occasion partially crystallised. When this material was gently warmed with acetic anhydride (5 ml.) and sodium acetate (1·5 g.) for 15 minutes, and the mixture treated with water (25 ml.), the *dinitrodiacetoxystyrene* (III) (2·6 g.) separated and was collected 1 hour later, and well washed with water. The diacetate, which had m. p. 128—132° (sintering at 124°) and was sufficiently pure to be used in the next stage of the synthesis, was recrystallised from aqueous alcohol, forming slender,

* Thorough washing at this stage with ice-cold aqueous sodium hydrogen carbonate and then with cold water to remove traces of nitric acid decreased the yield of nitroaldehyde considerably.

elongated, pale orange needles, m. p. 133—134° (sintering at 130°) (Found: C, 46·2; H, 3·4. $C_{12}H_{10}O_8N_2$ requires C, 46·45; H, 3·2%).

5 : 6-*Dihydroxyindole* (V).—When a mixture of the foregoing dinitrodiacetoxystyrene (2 g.), iron powder (10 g.), acetic acid (40 ml.), and absolute alcohol (50 ml.) was gently warmed, a vigorous reaction ensued and this was maintained for 11—12 minutes by occasional heating. The reaction mixture was filtered, the solid washed with small portions of hot alcohol, and the filtrate diluted with water, basified with solid sodium hydrogen carbonate, and extracted five times with ether. Evaporation of the combined dried extracts left a viscous gum which on being kept in a vacuum partially crystallised and was then purified by being extracted several times with hot light petroleum (b. p. 60—80°) containing 20% of benzene., On being kept, the combined extracts deposited 5 : 6-*diacetoxyindole* (0·80 g.), m. p. 130—133° (sintering at 124°), and a further quantity (75—100 mg.) was obtained by concentration of the light petroleum filtrate. Recrystallised from benzene–light petroleum (b. p. 60—80°) (charcoal), this compound (1 g.) formed compact hemispherical clusters of prisms (0·82 g.), m. p. 134—136°, giving strongly positive reactions with the Ehrlich and the nitroprusside reagent (Found: C, 61·5; H, 4·9; N, 6·3. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·7; N, 6·0%).

A solution of 5 : 6-diacetoxyindole (0·2 g.) in methanol (5 ml.) at 0° was added to a mixture of sodium hydrosulphite (dithionite) (1 g.) in 10% aqueous sodium hydroxide (5 ml.) kept at 0°, the reaction vessel was closed, and the mixture was vigorously agitated until the purple colouration originally assumed by the solution had disappeared, and then kept at 0° for 15 minutes. After the addition of acetic acid (1 ml.) in water (7 ml.) the resulting pale yellow solution was diluted with water (50 ml.) and extracted several times with ether. The following operations were then carried out in an atmosphere of nitrogen. The combined extracts (*ca.* 50 ml.) were dried over sodium sulphate admixed with a little sodium hydrosulphite, and concentrated to about ½ of the original volume, and the residual liquor was mixed with light petroleum (b. p. 60—80°) (25 ml.) and further concentrated until a small amount of a reddish amorphous material was precipitated; this solid was removed and the liquor was then evaporated until crystalline material began to separate. On being kept, the residue deposited 5 : 6-*dihydroxyindole* (60 mg., 46% of theoretical yield), m. p. 137—138°, which was collected without special precautions and on recrystallisation from benzene–light petroleum (b. p. 60—80°) formed glistening, colourless needles, m. p. 140° (decomp.) (Found: C, 64·7; H, 4·9; N, 9·4. $C_8H_7O_2N$ requires C, 64·4; H, 4·7; N, 9·4%). This compound, which is readily soluble in alcohol, ether, and acetone, appreciably soluble in warm benzene or cold water, and insoluble in light petroleum, gives a deep red colouration with Ehrlich's reagent at room temperature and an intense green ferric reaction in alcohol. On the addition of a drop of aqueous sodium hydroxide an aqueous solution of the indole containing sodium nitroprusside rapidly assumes a dark brown colour which changes to a dirty green on the addition of dilute acetic acid. When stored in a tightly stoppered specimen tube 5 : 6-dihydroxyindole darkens perceptibly in about 14 days, but on exposure to the atmosphere the surface of the crystals becomes dark in the course of 6—8 hours. Solutions of the substance in benzene, ether, or dilute acetic acid are moderately stable, but in tap water a blue colouration appears in the course of a few minutes, whilst the addition of a trace of sodium hydrogen carbonate to an aqueous solution causes rapid oxidation to take place. In the latter case the initially colourless solution becomes violet, and then deep bluish-purple, and eventually a granular black melanin-like precipitate forms.

5 : 6-*Dimethoxyindole*.—5 : 6-Diacetoxyindole (0·2 g.), was deacetylated in the foregoing manner, methyl sulphate (1 g.) was added to the alkaline solution, and the mixture was vigorously agitated in the absence of air for ½ hour, acidified with dilute acetic acid, and extracted with ether. The residue left on evaporation of the dried extracts was digested with boiling light petroleum (b. p. 60—80°), and on being concentrated, the extract deposited 5 : 6-dimethoxyindole in clusters of colourless slender needles, m. p. 142—146°, which on being sublimed in a vacuum at 100—110°/0·05 mm., afforded the pure compound, m. p. 154—155° unchanged on recrystallisation (Found: C, 67·6; H, 6·0. Calc. for $C_{10}H_{11}O_2N$: C, 67·8; H, 6·2%).

β : 2-*Dinitro*-4 : 5-*diacetoxy*-β-*methylstyrene*.—The condensation of 2-nitroprotocatechuic aldehyde (4 g.) with nitroethane (2·8 g.) was effected with potassium hydroxide (3 g.) in 95% alcohol at −10° by the method employed in the case of nitromethane. The mixture was then diluted with an equal volume of water, kept at 0° for 2 days, and thoroughly extracted with ether. Evaporation of the ethereal extracts left the desired product mixed with unchanged aldehyde. This mixture was treated with concentrated aqueous sodium hydrogen sulphite (approx. 50 ml.) for 1 hour, and the required nitro-alcohol isolated by extraction with ether and converted by means of warm acetic anhydride (5 ml.) and sodium acetate (2 g.) into β : 2-*dinitro*-4 : 5-*diacetoxy*-β-*methylstyrene* as in the case of the lower homologue. Triturated with a little cold 95% alcohol, this product was obtained as a colourless powder (1·8 g.) sufficiently pure for conversion into the indole. Crystallised from benzene–light petroleum (b. p. 60—80°), the dinitrostyrene formed fluffy aggregates of colourless slender needles, m. p. 119° (Found: C, 47·8; H, 3·6. $C_{13}H_{12}O_8N_2$ requires C, 48·2; H, 3·7%).

Unchanged aldehyde (1·3 g.) was recovered in the usual manner from the sodium hydrogen sulphite liquors which had been exhausted with ether.

5 : 6-*Dihydroxy*-2-*methylindole* (V, R = Me).—Simultaneous reduction and cyclisation of the foregoing dinitrostyrene (1 g.) by the procedure employed for the lower homologue (III, R = H) gave 5 : 6-*diacetoxy*-2-*methylindole* (IV, R = Me) (0·3 g.), which separated from benzene–light petroleum (b. p. 60—80°) (1 : 2) in compact clusters of colourless, short, stout needles, m. p. 134°, giving with cold Ehrlich reagent an intense red colouration tinged with blue (Found: C, 63·0; H, 5·2; N, 5·9. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7%).

Deacetylation of the foregoing diacetate (0·2 g.) with aqueous sodium hydroxide containing sodium hydrosulphite according to the method employed for (IV, R = H) gave 5 : 6-*dihydroxy*-2-*methylindole* (0·09 g.) which crystallised from benzene–light petroleum (b. p. 60—80°) in colourless blades, beginning to darken at 180° and becoming black at 200° when heated in a sealed melting-point tube (Found: C, 66·3; H, 5·4; N, 8·3. $C_9H_9O_2N$ requires C, 66·3; H, 5·5; N, 8·6%). This compound, which exhibits an Ehrlich reaction similar to that given by the diacetate, gives an olive-green colouration with

alcoholic ferric chloride, rapidly changing to brown. Like the parent 5 : 6-dihydroxyindole (V, R = H) the 2-methyl derivative readily oxidises in aqueous solution containing a little sodium hydrogen carbonate, forming a reddish-brown solution. In organic solvents, *e.g.*, benzene, the substance gradually develops a pink colouration and appears to be somewhat less stable than (V, R = H).

β : 2-*Dinitro*-4-*acetoxy*-5-*methoxystyrene*.—Powdered 6-nitrovanillin (Raiford and Stoesser, *J. Amer. Chem. Soc.*, 1928, **50**, 2559) (0·5 g.), suspended in alcohol (25 ml.), was condensed with nitromethane (0·2 g.) by means of potassium hydroxide (0·3 g.) in the course of 12 hours, and the product, isolated by the general method, was heated with acetic anhydride (2 ml.) and sodium acetate (1·5 g.) until the mixture boiled, and then on the steam-bath for 15 minutes. After the decomposition of the excess anhydride with water the *dinitro-styrene* was isolated, dried, and crystallised from alcohol, forming pale yellow prisms (0·32 g.), m. p. 188° (Found : N, 9·7. $C_{11}H_{10}O_7N_2$ requires N, 9·9%).

6-*Hydroxy*-5-*methoxyindole*.—On reduction and cyclisation by the standard procedure the foregoing dinitro-styrene (0·5 g.) was converted into 6-*acetoxy*-5-*methoxyindole* which was obtained as a brown glass. Extraction of the latter with boiling light petroleum (b. p. 80—100°) gave the pure substance, which separated from the cooled extract in colourless needles (190 mg.), m. p. 135° (Found : N, 7·1. $C_{11}H_{11}O_3N$ requires N, 6·8%). Deacetylation of this derivative (100 mg.) was effected by the methyl alcoholic-ammonia process (*J.*, in the press), giving 6-*hydroxy*-5-*methoxyindole*, which formed flocculent needles (25 mg.), m. p. 111°, from light petroleum (b. p. 80—100°), having an intense reddish-violet ferric reaction in alcohol (Found : C, 66·4; H, 5·4; N, 8·5. $C_9H_9O_2N$ requires C, 66·3; H, 5·5; N, 8·6%). It was subsequently found that the sodium hydroxide–sodium hydrosulphite method of deacetylation gave a superior yield of the hydroxyindole (45 mg. from 100 mg. of acetate). A solution of this monomethyl ether in very dilute aqueous sodium hydrogen carbonate develops a purplish tint in about 3 minutes which changes to deep purple in about 10 minutes, whereas in phosphate buffer solution at approximately pH 8 the indole slowly oxidises giving a dark precipitate.

5-*Hydroxy*-6-*methoxyindole*.—From 6-nitro*iso*vanillin (Pschorr, *Ber.*, 1902, **35**, 4396) *β* : 2-*dinitro*-5-*acetoxy*-4-*methoxystyrene* was prepared by the standard route (yield, 70% of theoretical) and on crystallisation from alcohol formed pale yellow plates, m. p. 162° (Found : N, 9·9. $C_{11}H_{10}O_7N_2$ requires N, 9·9%). This substance was converted into 5-*acetoxy*-6-*methoxyindole* (yield, 63% of theoretical), which separated from light petroleum (b. p. 80—100°) in colourless glistening plates, m. p. 118° (Found : N, 6·8. $C_{11}H_{11}O_3N$ requires N, 6·8%). Deacetylation of this derivative by the methyl-alcoholic ammonia process and by the aqueous sodium hydroxide–sodium hydrosulphite method gave the same yield (63% of theoretical) of 5-*hydroxy*-6-*methoxyindole*, forming colourless needles, m. p. 113°, from light petroleum (b. p. 60—80°), which gave a brown ferric reaction in alcohol (Found : C, 66·3; H, 5·5; N, 8·3. $C_9H_9O_2N$ requires C, 66·3; H, 5·5; N, 8·6%).

A solution of this indole in very dilute aqueous hydrogen carbonate assumes a very faint pink tint in the course of 35 minutes, but a phosphate buffer solution at about pH 8 is relatively stable, and does not become coloured within 3 hours.

The authors are indebted to Messrs. Imperial Chemical Industries Limited for a grant in aid of this investigation.

UNIVERSITY OF LIVERPOOL. [*Received, January 29th*, 1948.]

---

453. *The Thermal Decomposition of* n-*Hexane.*

By R. G. PARTINGTON and C. J. DANBY.

The thermal decomposition of *n*-hexane has been further investigated.

On the basis of the hypothesis that the nitric oxide-inhibited reaction represents a molecular reaction, the relative probabilities for the initial rupture of the chain at various links are $C_{1-2} : C_{2-3} : C_{3-4} :: 3·9 : 2·5 : 1$. When the C_{2-3} break occurs the chances are more than 10 : 1 that ethane and butene-1 will be formed rather than ethylene and butane.

The total analysis of the products is consistent with the measured rates of the primary and of various consecutive reactions.

VARIOUS problems connected with the thermal decomposition of hydrocarbons must still be regarded as incompletely solved. Among them are the following : (*a*) the question whether the residual reaction measurable when the rate has been reduced to a limiting value by added nitric oxide represents a molecular reaction or some kind of chain reaction which persists in spite of the inhibitor, (*b*) the modes of breaking of the hydrocarbon chain in the primary process. It is proposed to subject these matters to some further experimental study. The present paper deals with *n*-hexane.

Among previous studies on *n*-hexane are those of Dintzes and Frost (*J. Gen. Chem. Russia*, 1933, **3**, 747) made, however, before the chain mechanism had been established, and of Hobbs and Hinshelwood (*Proc. Roy. Soc.*, 1938, *A*, **167**, 447), which was of a summary character only, the behaviour of hexane being compared with that of several other hydrocarbons in respect of apparent chain length. The theoretical considerations of Kossiakoff and Rice (*J. Amer. Chem. Soc.*, 1943, **65**, 590) should be mentioned in this connexion, as also should a detailed experimental study by Steacie and Folkins on the decomposition of *n*-butane (*Canadian J. Res.*, 1940, **18***B*, 1).

Experimental.

(i) *Determination of Decomposition Rate.*—The hexane was decomposed in a silica bulb of about 250 c.c. capacity maintained at a constant temperature in an electric furnace. It was connected to a capillary mercury manometer, to storage vessels for reactants, and to the usual system of high-vacuum pumps. Temperatures were measured by a platinum–platinum-rhodium thermocouple and potentiometer. To prevent condensation of hexane, the connecting tubes and manometer were wound with resistance wire and electrically heated. The reaction was followed by measurements of pressure change. The pressure–time readings were plotted, and the exact initial pressures and initial rates obtained from the graph by extrapolation and tangent-drawing respectively.

(ii) *Analysis of Reaction Products.*—For the collection of samples of product the apparatus was provided with a Toepler pump by which the contents of the reaction vessel could rapidly be withdrawn. When the hexane in the reaction vessel had decomposed to a given extent, as indicated by the pressure change, the gases were removed for analysis. By combining the products from about 50 separate experiments some 2—3 c.c. of condensed material (including unchanged hexane) were obtained.

The products from the decomposition of hexane may potentially contain all the straight-chain paraffin and olefin hydrocarbons having six carbon atoms or less, together with hydrogen. To carry out a complete analysis of such a mixture by low-temperature fractional distillation would be difficult and would require considerable quantities of material. Fractionation was therefore only employed to separate the mixture into a series of fractions having b. p.s separated by about 40°, each of which was then further investigated by other methods.

The products withdrawn from the reaction bulb by means of the Toepler pump were passed through two traps cooled with liquid air. The uncondensed fraction (consisting of methane with a little hydrogen) was collected in an evacuated bulb of known volume. The total amount of this fraction was determined by measuring its temperature and pressure. A sample was then taken from it for analysis by means of a Bone and Wheeler apparatus, the hydrogen being determined by oxidation over copper oxide at 275°, and the methane by combustion with excess of oxygen. The condensed fractions in the traps were combined and transferred by distillation to the still-pot of a glass low-temperature distillation apparatus. The column was of 8-mm. internal diameter and about 60 cm. long and was packed with rings of stainless-steel gauze. The reflux condenser consisted of a pointed copper rod which was passed into the upper part of the column through a rubber joint and was cooled by the introduction of liquid air, solid carbon dioxide and acetone, or freezing mixtures into a lagged metal cup soldered to its upper end. The temperature of the rod was measured by means of a copper–constantan thermocouple soldered to it. The whole column was contained inside a glass jacket which was continuously evacuated. The column was provided with a manometer, and distillations were carried out at atmospheric pressure.

The reflux condenser was first cooled with liquid air and the column operated under total reflux until the packing was thoroughly wetted, the still-pot being warmed, as required, by a small electric heater.

The temperature of the reflux condenser was then raised and three fractions were taken off successively. These were: ethylene and ethane (b. p.s −104° and −89°), propylene and propane (b. p.s −48° and −42°) and butene-1 and butane (b. p.s −6° and −1°). The fractions were collected in a trap cooled in liquid air and were distilled into separate bulbs of known volume, where their temperature and pressure were measured. Samples were taken from each fraction, and the ratio of saturated to unsaturated hydrocarbon determined in the Bone and Wheeler apparatus. (Concentrated sulphuric acid containing silver sulphate was used as an absorbent for ethylene, 87% sulphuric acid for the higher olefins.) The residue in the still-pot (consisting of unchanged hexane together with traces of C_5 and C_4 hydrocarbons which had not been separated) was distilled into a weighed tube closed by a tap and its amount determined by direct weighing. This fraction was analysed by adsorption on a charcoal column and fractional desorption with amyl acetate vapour by a technique derived from that of Claesson (*Arkiv Kemi Min. Geol.*, 1942, **15**, *A*, 1; The Svedberg Mem. Vol., 1942, p. 82). This analysis was carried out by Mr. C. S. G. Phillips, who is engaged upon a general study of the method. From a knowledge of the total amount and composition of each fraction the complete analysis of the product was calculated.

Considerable modifications in the distillation apparatus and technique were made as the result of trial analyses. A series of experiments was also made with synthetic mixtures, from the results of which a correction could be made for the fact that under the standard conditions used the unsaturated hydrocarbon in a saturated–unsaturated mixture was incompletely adsorbed by the reagent. With the method finally adopted the figures below were found in a trial analysis on a 5-component mixture of known composition.

	C.c. taken.	C.c. found.		C.c. taken.	C.c. found.
Ethylene	15	14	Butene-1	27	27
Ethane	17	17	Butane	14	14
Propane	27	28			

Experimental Results.—Influence of nitric oxide. An investigation was made of the dependence of the initial rate of decomposition on the pressure of added nitric oxide. With 95 mm. of *n*-hexane at 570° the initial rate fell to a steady limit reached with about 12 mm. of nitric oxide. The ratio of the rate of decomposition in the absence of nitric oxide to the limiting rate was 1·75 (Table I).

Table I.

Influence of nitric oxide.

95 Mm. of *n*-hexane; 570°.

Pressure of NO (mm.)	0	2·0	3·9	5·0	9·3	11·5	16·0	20·0
Initial rate (mm./min.)	31·8	29·8	23·3	24·0	23·1	18·3	18·2	18·1
Initial rate (relative)	1·00	0·94	0·73	0·75	0·73	0·58	0·57	0·57

TABLE II.

Influence of hexane pressure.

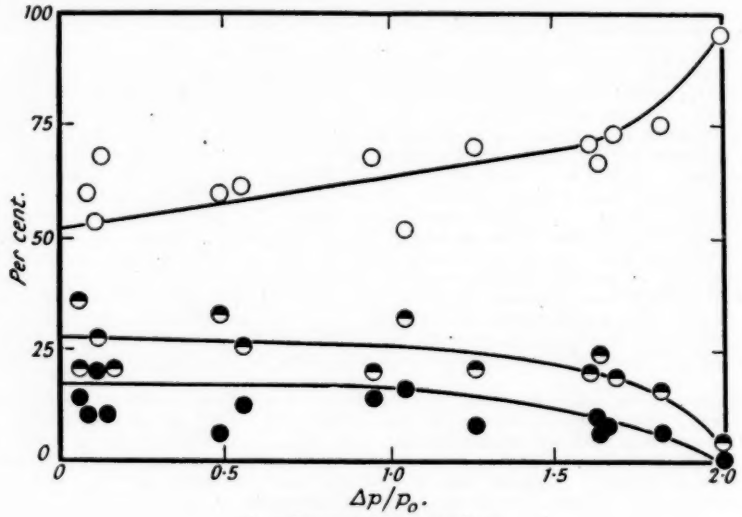
No nitric oxide present; 535°.

Initial press. of hexane (mm.)	3·4	7·2	25·0	34·0	46·0	94·0	108·3	115	144	171
Initial rate (mm./min.)	0·08	0·3	2·1	2·9	5·8	9·1	11·3	13·7	16·5	22

15 Mm. of nitric oxide; 536°.

Initial press. of hexane (mm.)	15·5	20·0	33	48·5	60	133	151	184
Initial rate (mm./min.)	0·18	0·22	0·39	0·62	1·0	3·2	3·8	6·8

Influence of initial pressure of n-*hexane.* The influence of the initial pressure on the initial rate of decomposition, both without nitric oxide and with 15 mm., is shown in Table II. A logarithmic plot revealed that in the absence of nitric oxide the initial rate was directly proportional to the initial pressure over the range 30—180 mm. Below 20 mm., however, the first-order rate constant falls off. With 15 mm. of nitric oxide the initial rate varied with (initial pressure of *n*-hexane)$^{1\cdot5}$.



○ = *Saturated hydrocarbons.*
◓ = *Ethylene.*
● = *Higher olefins.*

The rate constants are expressed by the relations

$$k = \left(\frac{dv_0}{dp_0}\right)_{p_0 = 100\text{ mm.}} \qquad \text{where } v_0 = \left(\frac{d(\Delta p)}{dt}\right)_{\Delta p = 0}$$

Influence of temperature on the initial rate of decomposition. Measurements were made, with and without nitric oxide, of the initial rate of decomposition over the temperature range 500—620°. At each temperature measurements were made at three different initial pressures (50, 100, and 150 mm.). The results are shown in Table III. From the graph of ln ($k \times 10^3$) against $10^3/T$, it was found that for the decomposition of *n*-hexane in the absence of nitric oxide:

$$\ln k = 33{\cdot}4 - (56{\cdot}8 \times 10^3)/RT$$

and for the decomposition in the presence of 15 mm. of nitric oxide:

$$\ln k = 42{\cdot}9 - (74{\cdot}0 \times 10^3)/RT$$

k is in min.$^{-1}$, R in g.-cals./mol./°c.

Analysis of Products.—A survey was first made of the way in which the ratio of ethylene to higher olefins (propylene + butene) in the products varied with the extent of the decomposition and with the temperature. For these analyses the gases from the reaction vessel were withdrawn through a trap cooled to 0° into vessels from which they could be transferred to the Bone and Wheeler apparatus. The results are shown in the figure. Although not of great accuracy, they showed that the composition of the products taken when $\Delta p/p_0 = 0{\cdot}5$ would approximate to the composition at zero decomposition. Moreover, the composition of the products was not seriously affected by temperature or by the addition of the nitric oxide.

Four separate analyses were made of the products from the decomposition of 200 mm. of *n*-hexane in the presence of 10 mm. of nitric oxide at 530°, the combined material from about 50 runs with $\Delta p/p_0 = 0{\cdot}5$ being taken in each case. The results are shown in Table IV.

TABLE III.

Influence of temperature.

Series 1.						
Temp., °c.	502	515·5	554·5	579·5	603·5	618·5
$k \times 10^3$ (min.$^{-1}$) at 100 mm. initial pressure :						
without NO	32	52	260	830	1960	2400
with 15 mm. NO	2·6	10·0	135	460	1300	1840
Series 2.						
Temp., °c.	512	534	535·5	571·0	588	
$k \times 10^3$ (min.$^{-1}$) with 15 mm. NO	11	25	23	290	650	

TABLE IV.

Uncorrected analyses (% *by vol.*).

					Mean.
Hexane	51·6	49·7	39·5	40·6	45·4
Butane	0·9	0·5	0·3	0·6	0·6
Butene	2·4	2·4	6·4	3·2	3·6
Propane	1·8	1·7	1·8	1·5	1·7
Propylene	5·6	11·9	14·2	13·3	11·2
Ethane	8·2	5·4	6·6	10·9	7·8
Ethylene	14·0	13·5	19·0	15·7	15·5
Methane	—	—	(11·1)	13·2	13·2
Hydrogen	—	—	0·7	0·9	0·9
Methane + hydrogen	15·5	14·9	11·8	14·1	14·1

During the distillation it was difficult to judge when all the C_4 fraction had come off. The residue was therefore analysed by the fractional desorption method referred to above. Mr. Phillips's results were as follows :

Residue contained:

C_6 compounds ..... 89·3% of total C_5 compounds ..... 2·1% C_4 compounds ..... 8·6%.

When account is taken of these results and the superior accuracy of the third and fourth fractionations allowed for, the figures for the composition of the products are as follows :

Component.	% by vol.	Component.	% by vol.
Hexane	39·7	Propylene	12·2
Pentene	1·0	Ethane	7·8
Butane	0·6	Ethylene	15·5
Butene	7·4	Methane	13·2
Propane	1·7	Hydrogen	0·9
			100·0

In making the correction the C_4 fraction found in the desorption experiment was taken to be butene, since the proportion of butane in the main fraction was extremely small. The C_5 fraction was taken to be pentene, pentane being very unlikely on chemical grounds.

DISCUSSION.

The inhibition by nitric oxide of the decomposition of *n*-hexane indicates that free radicals play a part in the mechanism of the reaction. The value of 1·75 obtained for the mean chain length at 570°, and for an initial pressure of 95 mm., is in fair agreement with other values obtained by Hobbs and Hinshelwood.

Mean chain length and temperature. The values obtained in this investigation for the energy of activation of the decomposition at 100 mm. initial pressure were :

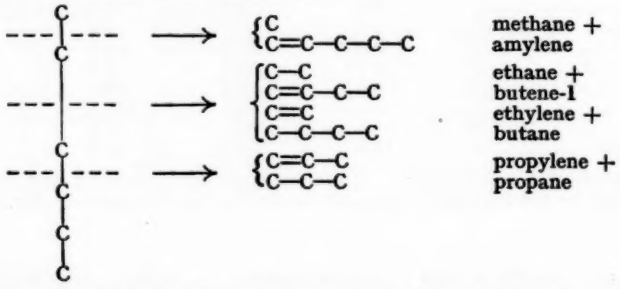
for the normal decomposition, 58·8 kcals./mol.
for the inhibited reaction, 74·0 kcals./mol.

The fact that these differ means that the mean chain length is dependent on temperature, the values showing that it increases as the temperature falls. This general effect (the dependence of mean chain length on temperature) has been discussed by Staveley and Hinshelwood (*J.*, 1937, 1568). The uninhibited *n*-hexane decomposition is approximately of the first order.

The observation that the rate of the fully inhibited reaction varies approximately as $(p_{\text{hexane}})^{1·5}$—which is in agreement with the finding of Hobbs and Hinshelwood—is a result which must be explained. There is no evidence that the 1·5 power law is valid over a wide range, and it may merely be an approximation for the transition from the first order to second order with falling pressure which would be observed if the residual reaction were unimolecular

and if the chains were all suppressed. On the other hand, a tentative suggestion was considered by Hobbs and Hinshelwood, namely, that the residual inhibited reaction could itself depend on a special type of chain reaction with carriers immune to the attack of nitric oxide. Steacie and his associates have, in fact, found that the decomposition of *n*-butane (which is theoretically very similar to that of *n*-hexane) could be initiated at low temperatures by free radicals from ethylene oxide, and that the sensitization persisted in the presence of large amounts of nitric oxide, showing that in this case the fully inhibited decomposition did not correspond to the complete suppression of chains.

Analytical results. In discussing the analytical results we shall, however, assume in the first instance that the steady rate attained in presence of the nitric oxide represents a reaction at least sufficiently free from chains to afford information about the primary positions of breaking of the hexane molecule. According to what was said above, the first step in the decomposition will be the rupture of one of the C–C bonds, leading to a rearrangement to a saturated and an unsaturated hydrocarbon. It was found by infra-red absorption of product samples that all the unsaturated hydrocarbons present had terminal double bonds, so there remain the following possible modes of rupture of the hexane molecule :



Preliminary measurements, including infra-red absorption, showed that the initial products contained ethylene, propylene, and butene-1, and that the proportions at the stage where $\Delta p/p_0 = 0{\cdot}5$ approximate to those at zero decomposition. They showed, moreover, that the formation of these three unsaturated hydrocarbons was in a large measure by simultaneous rather than by consecutive reactions.

In order, however, to be able to interpret the full analyses in more detail, auxiliary measurements were made of the rates of decomposition of the various product species. The results are given in Table V.

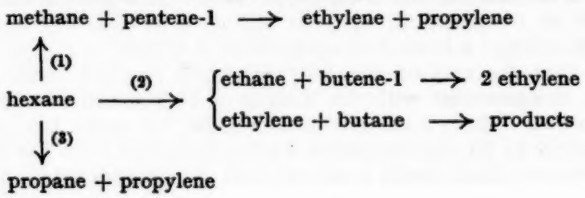
TABLE V.

Relative reaction rates of possible subsequent decompositions (approximate).

	$k \times 10^4$ (min.$^{-1}$) for fully inhibited reaction.	Apparent order of reaction over (limited) range studied.
Ethane	6	—
Propane	24	1·5
Butane	180	1·5
Pentane	240	1·4
Ethylene	(5) (polymerisation)	—
Propylene	18	1·6
Butene-1	210	1·5
Cf. *n*-hexane	250	1·4

Unfortunately, no pentene-1 was available, but from the results for propylene and butene-1 it is reasonable to assume that the value for k would be of the order of 10 times that for *n*-hexane; it was also assumed for the purposes of calculation that the decomposition of all these substances was of the order 1·5.

Neglecting the small amount of hydrogen, we may now consider the following scheme :



From the results in Table V it may be taken that during the time of the experiment the methane, ethane, ethylene, propane, and propylene did not undergo further change. The butene-1 and pentene-1 undoubtedly undergo some further decomposition. The case of butane is doubtful. A very rough estimate of the amount of decomposition undergone by the butane may be obtained as follows:

	Initial pressure of *n*-hexane	200 mm.
	Final pressure of mixture	300 mm.
	% Hexane in final mixture	40 (by analysis)
∴	Pressure of hexane	120 mm.
∴	Amount of hexane decomposed	80 mm.

Now the average pressure of butane was $\frac{\frac{1}{2} \times 0{\cdot}6}{100} \times 300 = 0{\cdot}9$ mm.

If the average pressure had been 200 mm., the amount decomposed would have been approximately $80 \times 180/250$. Thus the actual amount of decomposition would be of the order

$$80 \times \frac{180}{250} \times \left(\frac{0{\cdot}9}{200}\right)^{1{\cdot}5} = 0{\cdot}016 \text{ or } < 0{\cdot}01\%.$$

It can therefore be assumed that the butane does not decompose appreciably during the experiment.

The decomposition of the pentene-1 is very important and very nearly keeps pace with the formation, so that the ethylene and propylene into which it breaks down count practically, from the analytical point of view, as primary products. The amount of pentene-1, had there been no decomposition, should have been equivalent to the amount of methane, *i.e.*, 13·2%. But the amount found was 1·0%. Thus the amount decomposed = 13·2 − 1·0 = 12·2%. This should also be given by (propylene found − propylene equivalent to propane) = 12·2 − 1·7 = 10·5%.

According to the rate measurements, the amount of butene-1 which decomposes should be approximately:

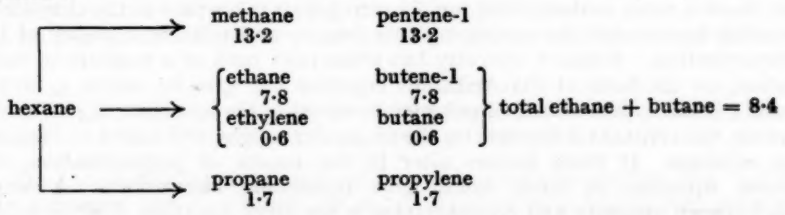
$$80 \times \frac{210}{250} \times \left(\frac{3{\cdot}7}{200}\right)^{1{\cdot}5} = 0{\cdot}17 \text{ or } 0{\cdot}06\%.$$

Thus the butene-1 analysis should give about 7·4 + 0·1 = 7·5, which agrees fairly closely with the value of 7·8 found for ethane.

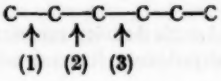
The ethylene present should be the sum of the following: 0·6 from that equivalent to the butane, 0·2 from the decomposition of butene-1, and 12·2 from the decomposition of pentene-1, *i.e.*, 13·0. The propylene should equal 12·2 from the pentene + 1·7 from that equivalent to the propane = 13·9. This scheme, with the observed reaction rates of these, leads to the analytical figures shown in the upper row of figures in the following table, whereas the lower row gives the

CH_4.	C_2H_6.	C_3H_8.	C_4H_{10}.	C_2H_4.	C_3H_6.	C_4H_8.	C_5H_{10}.
13·2	7·8	1·7	0·6	13·0	13·9	7·4	1·0
13·2	7·8	1·7	0·6	15·5	12·2	7·4	1·0

observed figures, which are in fair agreement. On this basis, the primary products would appear to be as follows:



The chances of the hexane molecule breaking in positions (1), (2), and (3) would thus appear to be in the ratio 13·2 : 8·4 : 2 × 1·7, or 3·9 : 2·5 : 1, the figure relating to position (3) being



doubled to allow for the fact that reactions at positions (1) and (2) have each two chances to contribute to the products. When the chain breaks in position (2) the chances are more than 10 : 1 that ethane and butene-1 will be formed rather than ethylene and butane.

Further comment and discussion is reserved until further experimental studies have been completed.

This work forms part of the programme of the Fuel Research Board of the Department of Scientific and Industrial Research, and this paper is published by permission of the Department.

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, February 18th*, 1948.]

---

454. *The Propagation of Reaction Chains in the Polymerisation of Styrene.*

By J. W. MENARY, A. R. UBBELOHDE, and M. J. WRIGHT.

Styrene has been polymerised in the presence of oxygen, nitrogen, hydrogen, and mixtures of oxygen with nitrogen and oxygen with hydrogen severally. By using special apparatus, the progressive viscosity and density changes resulting from polymerisation could be measured on the same sample without unsealing the reaction vessel.

A simple mathematical treatment is proposed, which combines the viscosity and density measurements, to give a measure of the molecular weight of the polymer being formed during the reaction. This molecular weight decreases in a characteristic way with increasing partial pressure of oxygen. No significant difference could be detected between the action of hydrogen and nitrogen, when pure. When acting as a diluent for the oxygen, some evidence was obtained that the hydrogen takes part in the chemistry of the polymerisation.

Calculated molecular weights are used to follow the propagation of reaction chains in the polymerisation of styrene. The effect of the partial pressure of oxygen is tentatively interpreted by a mechanism in which oxygen acts as a chain breaker, as well as initiating chains through the formation of peroxides.

OXYGEN appears to act sometimes as a promoter and sometimes as an inhibitor in addition polymerisation. The mechanism of promoter action is almost certainly related to peroxide formation. The inhibiting action has been explained by Barnes (*J. Amer. Chem. Soc.*, 1945, **67**, 217) as being due to preferential reaction of carriers in the reaction chain, with oxygen rather than with further molecules of monomer. The general effect observed is an initial induction period, followed by polymerisation catalysed by the vinyl peroxide formed during the induction period.

So far as is known, nitrogen molecules have no specific effect on the course of the polymerisation reaction. To investigate this more fully, comparative experiments were carried out in which the nitrogen was replaced by hydrogen. If energy transfer plays an important part in the propagation of the reaction chains, hydrogen might be expected to behave differently from nitrogen. Hydrogen has been shown to be about as effective in causing the activation of organic molecules in unimolecular decompositions as the organic molecules themselves (cf. Oldenberg and Frost, *Chem. Reviews*, 1937, **20**, 99) and would probably facilitate the degradation of vibrational energy in colliding with an activated reaction product. However, no evidence for any specific difference between pure nitrogen and pure hydrogen could be obtained, at least under the conditions of the experiments described below. When the hydrogen is used as a diluent for the oxygen, there is some evidence that, unlike nitrogen, it takes part in the chemical reactions.

The reaction was studied by measuring *both* density and relative viscosity of the styrene during polymerisation. Relative viscosity has often been used as a measure of the extent of polymerisation, on the basis of the Arrhenius equation $\log \eta_r = kc$, where η_r is the relative viscosity, and c is the concentration of polymer dissolved in the monomer (*e.g.*, Foord, *J.*, 1940, 48). However, the constant k depends on the molecular weight and degree of branching of the polymer in solution. If these factors alter in the course of polymerisation, the use of the Arrhenius equation by itself would give misleading information. A more general relationship between viscosity and concentration is the Mark equation, $KM^{\alpha} = [\eta] \simeq (\ln \eta_r)/c$, where $[\eta] = \underset{c \to 0}{\mathrm{Lt}} (\ln \eta_r)/c$ is the intrinsic viscosity, M the molecular weight of the polymer, and K and α are constants which depend to some extent on the degree of branching of the polymer molecules.

This relationship may be combined with density measurements as follows. Both experiment and theory indicate that the mass of polymer formed controls density changes, which do not

appear to be influenced to any great extent by the molecular weight or degree of branching of the polymer molecules.

Starkweather and Taylor (*J. Amer. Chem. Soc.*, 1930, **52**, 4708) showed that for vinyl acetate the extent of polymerisation is proportional to the volume contraction per cent., or to the increase in density divided by density, for

$$\text{Volume contraction, } \% = (\rho_t - \rho_0)/\rho_t = \Delta\rho/\rho_t$$

where ρ_0 = the density of monomer, ρ_t = density of partly polymerised monomer in time t, and $\Delta\rho$ = increase in density. For a small change in density $\Delta\rho/\rho_t \approx \Delta\rho/\rho_0$, so that in the initial stages of polymerisation the increase in density should measure the extent of reaction. Giguère (*J. Polymer Chem.*, 1947, **2**, 296) has shown this to be true up to 25% conversion by preparing solutions of polystyrene in monomer and measuring their density.

We may derive this theoretically: Let the volume of a styrene molecule be V c.c., its mass m g., and the initial number of molecules N; then initial density $\rho_0 = m/V$. Suppose that after time t, n new chemical bonds are formed by the polymerisation reaction. If the contraction in volume (v) per bond formed is constant and does not depend on the way the monomer units are joined together in the polymer molecule (*i.e.*, neglecting corrections for branching, etc.; cf. the general evidence of the parachor, Sugden, "Parachor and Valency", 1930, p. 33), then

Volume contraction at time	$t = nv$ c.c.
Density at time t	$\rho_t = Nm/(NV - nv)$
	$= \rho_0/\left(1 - \frac{nv}{NV}\right)$
Therefore	$n = NV\Delta\rho/v\rho$
Weight of polymer formed	$= nm$ g.
Concentration of polymer	$c = nm/(NV - nv)$
	$= m\Delta\rho/\rho_0 v = k\Delta\rho$ g./c.c.

which is the relation observed by Giguère, and by Starkweather and Taylor.

Combining this with Mark's relationship we have

$$(\log \eta_r)/\Delta\rho = K'M^a = \text{"Structure function"}$$

where K' is a constant and the other symbols are as before. Simultaneous measurement of viscosity and density during polymerisation permits evaluation of the "Structure function" $(\log \eta_r)/\Delta\rho$. From its variation can be seen how far the molecular weight and structure of the polymer alter during the course of the polymerisation.

The results of various polymerisation experiments are recorded in Figs. 1—4. Important features of these results are now discussed.

(i) Three experiments under pure nitrogen and two under pure hydrogen (Figs. 1A, 2A, 3A), showed that the behaviour of these two gases is similar, so far as the present experiments go. It will be seen that the curves obtained for one of the experiments in the presence of nitrogen lie well below those obtained for the other experiments with nitrogen or hydrogen present (Figs. 1A, 2A, and 3A). In this case there was evidence that the course of the reaction was substantially different since the styrene became opalescent when the polymerisation vessel was being sealed off. This experiment has not been included in the average below.

Both $\Delta\rho$ and $\log \eta_r$ increase linearly with time and the average slope for all the experiments was

(t in minutes)

$$\mathrm{d}(\log \eta_r)/\mathrm{d}t = 0{\cdot}00205 \pm 0{\cdot}00009$$
$$\mathrm{d}(\Delta\rho)/\mathrm{d}t = (3{\cdot}40 \pm 0{\cdot}12) \times 10^{-4}$$

On the other hand, the $\log \eta_r$ curve for polymerisation under oxygen (Fig. 1A) indicates a considerable induction period, whereas the $\Delta\rho$–t curve indicates hardly any induction period (Fig. 2A). As explained above, this is because, in addition to increasing the number of chemical bonds, as shown by $\Delta\rho$, the course of polymerisation involves changes of molecular weight and structure of the polymer. Viscosity is much more sensitive to these changes than is density.

(ii) Various mixtures of oxygen with nitrogen give curves lying between those obtained for the pure gases (Figs. 1B, 2B, 3B). So far as could be ascertained from a single series of experiments, hydrogen and nitrogen do not behave in the same way in the presence of oxygen.

FIG. 1A.

Viscosity increase with time for polymerisation in the presence of pure nitrogen, pure hydrogen, and pure oxygen.

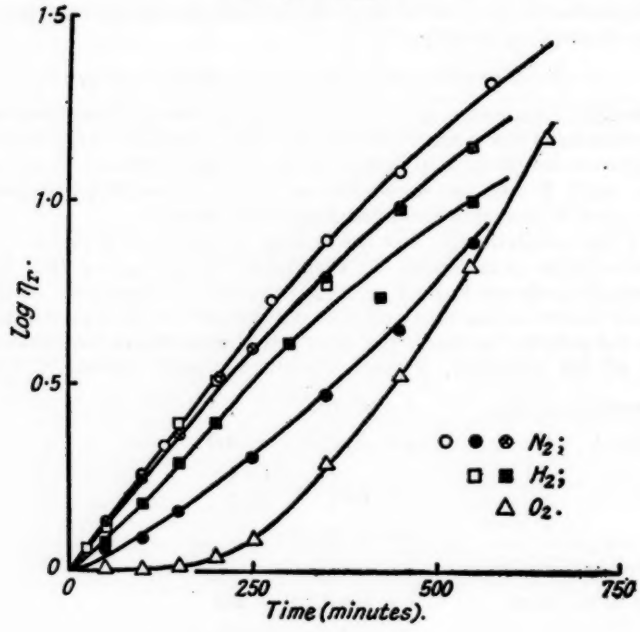
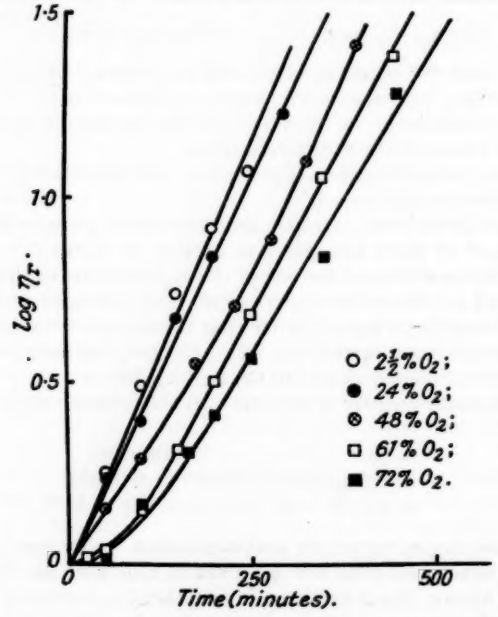


FIG. 1B.

Viscosity increase with time for polymerisation in the presence of mixtures of oxygen with nitrogen.



The difference is shown in Figs. 2B and 3B. The values of log η_r are not plotted in this case, to avoid confusing Fig. 1B, but these can be obtained from Figs. 2B and 3B by taking the ratios.

Some oxygen is consumed during the polymerisation, since on opening the viscometer at the completion of experiments with oxygen present there was an inrush of air, particularly noticeable

FIG. 2A.

Density increase with time for polymerisation in the presence of pure nitrogen, pure hydrogen, and pure oxygen.

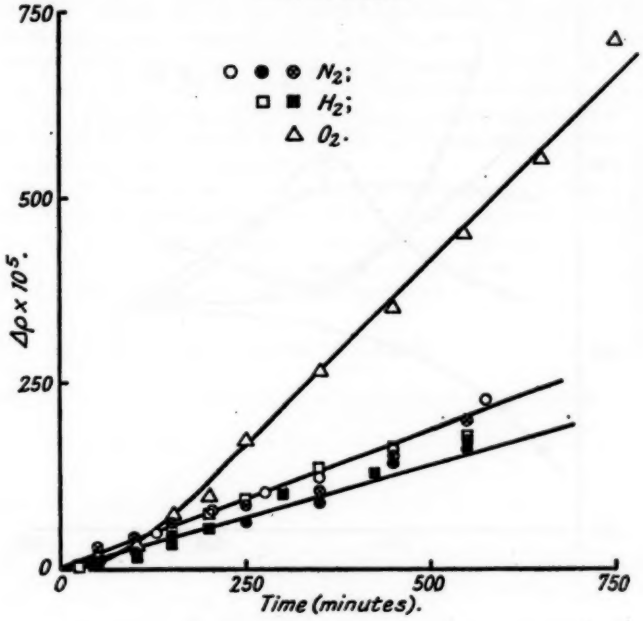


FIG. 2B.

Density increase with time for polymerisation in the presence of mixtures of oxygen with nitrogen, and oxygen with hydrogen.

Nitrogen mixtures:

○ $2\frac{1}{2}\%O_2$; ● $24\%O_2$; ⊗ $48\%O_2$;
□ $61\%O_2$; ■ $72\%O_2$;

Broken curve calculated for $7\%O_2$.

Hydrogen mixture: ▲ $7\%O_2$.

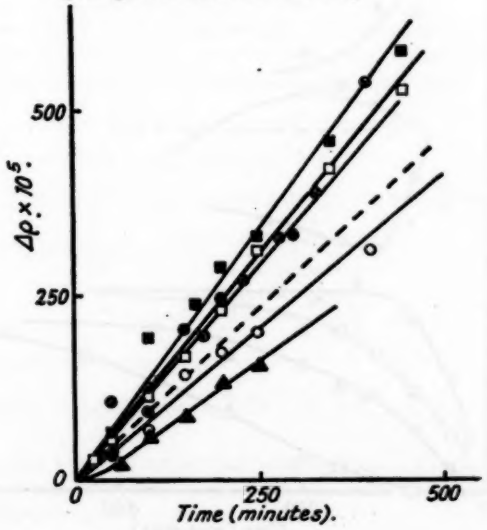


FIG. 3A.

Comparison between the effect of pure nitrogen and pure hydrogen on the structure function.

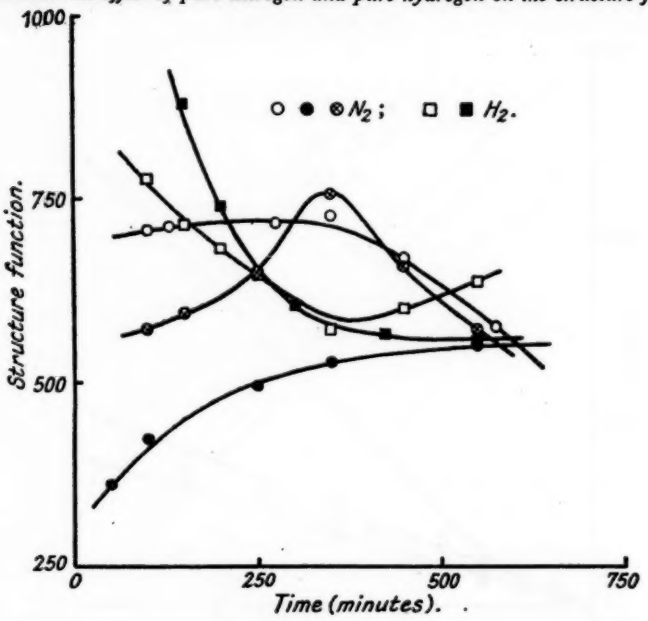
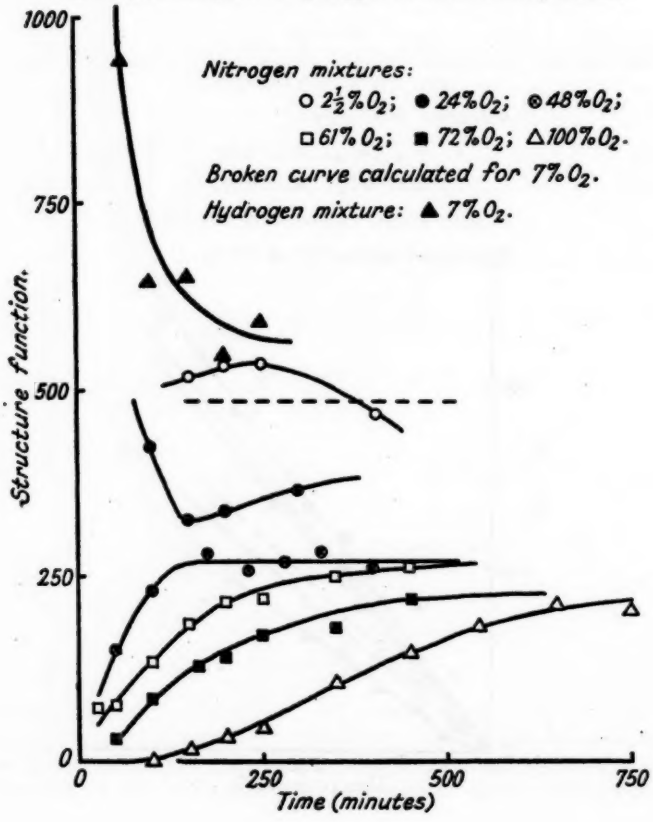


FIG. 3B.

The effect of partial pressure of oxygen on the structure function.



in experiments where more than 24% oxygen was used. This indicates consumption of oxygen during the reaction, which is to be expected if peroxides are formed.

Fig. 3 shows the plot of $(\log \eta_r)/\Delta\rho$ against time. So far as this "Structure function" measures the molecular weight of the polymer being formed, it appears that the molecular weight increases from zero to an asymptotic limit (Fig. 3B) provided that the atmosphere contains 48% oxygen or more. With less than this amount of oxygen present the molecular weight is higher (cf. also Fig. 3A). For each concentration of oxygen the limiting molecular weight is more or less constant. Plotting the partial pressure of oxygen against the *average value* of the limiting molecular weight gives a smooth curve (Fig. 4) falling steeply at low partial pressures of oxygen and flattening out at higher partial pressures.

Discussion.—Polymerisation in the presence of oxygen. A curve of this type (Fig. 4) may be interpreted by the following mechanism: Let M represent a monomer molecule, P an inactive polymer molecule, and A′ and R′ active growing polymer molecules. These can each have a molecular weight varying with time, but otherwise differ from one another merely in their origin. Then we may have the following series of reactions:

Initiation.

(1) $\mathrm{M} + \mathrm{M} \xrightarrow{k_{a_1}} \mathrm{A}'$ (thermal activation)

(2) $\mathrm{AO_2} \xrightarrow{k_{a_2}} \mathrm{R}'$ (activation of peroxide to start chains)

Propagation.

(3) $\mathrm{A}' + \mathrm{M} \xrightarrow{k_b} \mathrm{A}'$

(4) $\mathrm{R}' + \mathrm{M} \xrightarrow{k_b} \mathrm{R}'$

Cessation.

(5) $(\mathrm{A}' \text{ or } \mathrm{R}') + (\mathrm{A}' \text{ or } \mathrm{R}') \xrightarrow{k_{c_1}} \mathrm{P}$

(6) $(\mathrm{A}' \text{ or } \mathrm{R}') + \mathrm{O_2} \xrightarrow[\text{very rapid}]{k_{a_3}} \mathrm{AO_2}$

Active centres are formed either thermally or from the decomposition of peroxides according to equations (1) and (2). Owing to the preferential reaction of the active centres with oxygen [reaction (6)] little or no polymer will be formed until the concentration of dissolved oxygen has fallen to a low value. The concentration of the peroxide will therefore increase until substantially all the oxygen has been combined. The molecular weight of the polymer will then start to increase rapidly as the second cessation reaction will then become relatively unimportant. In the above experiments the volume of styrene and the volume of the gaseous atmosphere were kept approximately constant so the ultimate concentration of peroxide formed may be taken as proportional to the initial partial pressure of oxygen in the polymerisation vessel. On the basis of this assumption the limiting value

$$[\mathrm{AO_2}] = Kp_{\mathrm{O_2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Other workers have shown that the concentration of peroxide catalysts remains sensibly constant during polymerisation owing to their slow unimolecular decomposition. A steady state is reached when (A′ and R′ being treated as kinetically equivalent)

$$\text{Rate of initiation} = \text{rate of cessation}$$

$$k_{a_1}[\mathrm{M}]^3 + k_{a_2}Kp_{\mathrm{O_2}} = k_{c_1}[\mathrm{A}']^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

i.e., only reactions (1), (2), and (5) are taken into account in the steady state.

$$\text{Chain length} = \frac{\text{Rate of propagation}}{\text{Rate of cessation}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

$$= \frac{k_b[\mathrm{A}'][\mathrm{M}]}{k_{c_1}[\mathrm{A}']^2} = \frac{k_b[\mathrm{M}]}{k_{c_1}[\mathrm{A}']}$$

Substituting from equation (8), we have

$$\text{chain length} = k_b[\mathrm{M}]/\sqrt{k_{c_1}(k_{a_1}[\mathrm{M}]^3 + k_{a_2}Kp_{\mathrm{O_2}})} = \frac{K_1}{\sqrt{1 + K_2 p_{\mathrm{O_2}}}}$$

The chain length, *i.e.*, the average molecular weight once a steady state has set in, should thus behave as is actually observed in Fig. 4, in which the limiting molecular weight is controlled by the initial partial pressure of oxygen used.

Effect of hydrogen in the presence of oxygen. The data so far available require further experimental substantiation before a definite interpretation can be given. However, the possibility of interference with the normal polymerisation chains, by processes involving the chemical interaction of hydrogen such as $AO_2 + H_2 \longrightarrow A{\cdot}O{\cdot}OH + H$, is of considerable interest, and should be kept in mind in other experiments on polymerisation. Such a possibility of chemical interaction with the radicals in solution is not necessarily limited to hydrogen. For example, hydrocarbons such as ethylene can be considered from this standpoint.

By controlling the temperature and partial pressure of oxygen used, the average molecular weight of the product may likewise be controlled, as is shown by Fig. 4.

The general rise of molecular weight with time when the partial pressure of oxygen exceeds about 24% (Fig. 3B) also agrees with the simple mechanism outlined. However, when the partial pressure of oxygen is less than about 24%, the course of polymerisation, at the temperature used, is more erratic, and high *initial* molecular weights are frequently found. These high initial molecular weights appear to be due to the absence of reaction (6) which suppresses polymer molecular weight in the early stages, when sufficient oxygen is present. In the absence of this reaction, the polymer molecules grow until they interfere with one another. But the reproducibility of the growth process is poor, as might be expected from the fact that chain stopping and chain starting depend on chance impurities.

FIG. 4.

The effect of partial pressure of oxygen on the limiting value of the structure function.

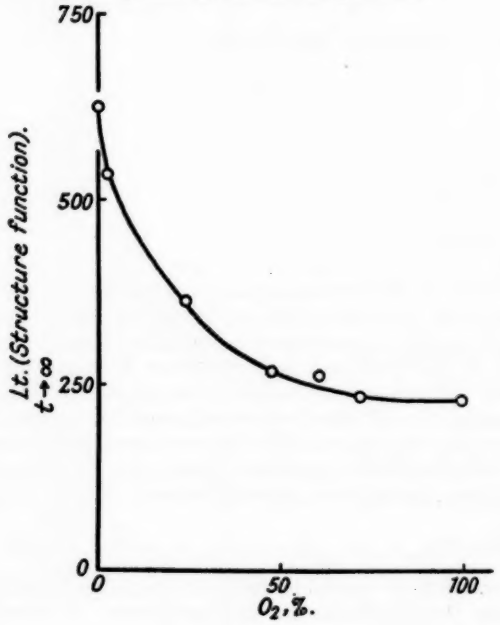
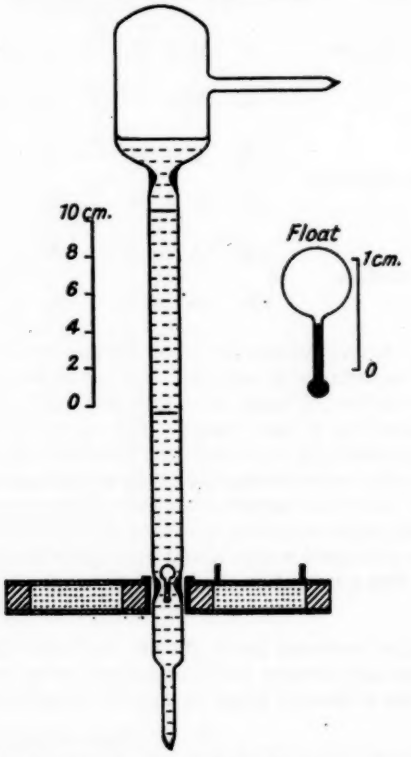


FIG. 5.

Densitometer-viscometer in position for viscosity measurement.



An independent check on the above conclusions was obtained as follows. In some experiments the polymer formed was precipitated from benzene solution by the dropwise addition of excess of methylated spirits (Foord, *loc. cit.*). The polymer was filtered off and dried. An approximate value of the intrinsic viscosity was obtained by measuring the relative viscosity of solutions of the polymer in toluene (0·1—0·2%). The following results were obtained :

Gas present during polymerisation.	$[\eta]$.	Gas present during polymerisation.	$[\eta]$.
61% O_2 in N_2	1·13	48% O_2 in N_2	1·52
Pure H_2	2·66		

These results confirm the general trend towards increased molecular weight as the partial pressure of oxygen decreases.

Experimental.

Nitrogen.—Nitrogen as supplied by the British Oxygen Co. contained 1—2% of oxygen as the chief impurity. This was removed by the method employed by Mackle and Ubbelohde (this vol., p. 1161).

Oxygen.—The oxygen was also supplied by this firm, and was used without further purification.

Hydrogen.—Hydrogen was generated by electrolysis of a saturated solution of barium hydroxide, nickel electrodes being used. Purification was accomplished by passing the gas through two successive tubes packed with platinised asbestos electrically heated to 600°. The first tube served to remove traces of catalytic poisons which may have been present, and both tubes caused any adventitious oxygen to be oxidised to water. The purified hydrogen was dried by passing through concentrated sulphuric acid. Any sulphuric acid spray was removed by diffusion through potassium hydroxide pellets and chemically pure glass-wool.

Styrene.—On receipt, this contained quinol as inhibitor, together with an undetermined amount of phenylacetylene, a common impurity in commercial styrene. The scheme used for purification was essentially that of Price and Adams (*J. Amer. Chem. Soc.*, 1945, **67**, 1674). Quinol was removed by successive shaking with 10% sodium hydroxide solution. By stirring vigorously with Nessler's reagent (Johnson and McEwen, *ibid.*, 1926, **48**, 469) the phenylacetylene was removed. The product was allowed to stand over calcium chloride, and before use the styrene was fractionated from potassium hydroxide pellets under pure nitrogen at reduced pressure. The middle fraction was collected and redistilled as before, the fraction coming over at 45—46°/20 mm. being accepted as pure styrene.

The Viscometer–Densitometer.—Densities were measured by a magnetic balance method, the buoyancy force on a small glass float being counterbalanced by the magnetic force on a small piece of iron sealed into the float. Relative viscosities were obtained from the density of the liquid and the time of rise of the float between two marks on the viscometer tube. Since density and viscosity measurements do not appear to have been made simultaneously on a polymerising system, the method will be given in some detail.

Construction of the Apparatus.—The float. Pyrex tubing was drawn out to give a uniform capillary of about 2 mm. bore, and into this capillary was inserted a thin strip of "Stalloy" transformer core metal, chosen for this work because of its extremely low magnetic retentivity. One end of the capillary was sealed, and a small bulb of about $\frac{1}{4}$ in. diameter blown on the end. The other end of the capillary was thickened slightly and then sealed off giving the float a total length of about $\frac{1}{2}$ in. (Fig. 5). The density of the float was adjusted by adding small pieces of molten glass to the tail until the float just failed to sink in monomeric styrene at 25°. This ensured a high sensitivity for our work.

Densitometer–Viscometer. The vessel in which the polymerisation took place was a cylindrical bulb made from 2-in. Pyrex tubing. Joined to its were a $\frac{1}{16}$ in. diameter side-arm for filling, and a uniform $\frac{1}{4}$ in. (outside diameter) tube in which the measurements of density and viscosity were made. The float was inserted into this tube and kept in position by the constrictions as shown. Fig. 5 shows the apparatus in position for measurements of density and viscosity. During polymerisation, the apparatus was inverted so that the solution flowed into the large bulb.

Coil. Two thousand turns of 30 s.w.g. copper wire (enamelled and cotton-covered) were wound on a former made from a core of aluminium tubing of $\frac{1}{4}$ in. inside diameter and two plywood discs each 7 in. in diameter. The centre was reinforced by a circular block of wood fitting the aluminium core tightly. As the coil was intended to be immersed in a thermostat, the former was soaked in "Akard" bakelite lacquer and stoved for 3 hours in a vacuum oven. This was repeated after winding on the wire. The external leads were rubber-covered wire, and where they entered the coil the joins were well covered with "Picein" wax. The whole coil was finally given a thick coat of a mixture of one part bee's wax and one part resin, together with a little magnesium carbonate as filler. To concentrate the magnetic field of the coil, a ring of soft iron, of $\frac{1}{4}$ in. inside diameter, was attached to the upper end of the aluminium core. This served to give a sharper balance point in the density determination. The coil was clamped horizontally in a thermostat at 25° ± 0·02°. The current passing through the coil was measured by a linear scale milliammeter having a range of 150 ma.

Density calibration. Before insertion in the densitometer–viscometer the float was calibrated. The density ρ is given by $\rho = d + ki^2$, where d = density of the float, i = current through the coil, and k = constant. Several mixtures of ethyl acetate and chloroform containing up to about 5% of chloroform were prepared, and their density determined at 25° ± 0·02° with a pyknometer. A $\frac{1}{4}$ in. Pyrex tube sealed at one end was filled with one of these mixtures and clamped vertically in the thermostat through the centre of the coil. The float was dropped in, and 15—20 minutes allowed for the temperature to reach 25°. The current in the coil was switched on and adjusted to a value of about 120 ma. by means of the sliding resistance in parallel with it. The float was drawn down the tube by means of a magnet until it was held by the magnetic field of the coil. The current was then decreased slowly until the magnetic force just failed to balance the buoyancy force when the float commenced to rise to the surface. The current flowing when this occurred was noted and the procedure repeated several times for consistent results. Density ρ and i^2 gave a linear plot from which the constants d and k were calculated by standard probability methods. The float actually used for most of the experiments recorded here measured density according to the equation $\rho = 0{\cdot}89509 + 1{\cdot}562 \times 10^{-6}\, i^2$, where i was measured in milliamps.

The Polymerisation Experiments.—Freshly distilled styrene was quickly sucked into the inverted viscometer–densitometer and the air was displaced by the gas under which it was required to carry out the polymerisation. In the case of gases which were available in quantity (oxygen and nitrogen) this was done by blowing the gas through the vessel for about 10 minutes before sealing it off. For hydrogen and for the mixture of oxygen and hydrogen, which was prepared in a gasometer of 2 l. capacity, the vessel was evacuated and refilled with the gas, the process being repeated about a dozen times before

sealing off. About the same volume of styrene was taken (45 c.c.) in each experiment, so that the volume of the gas in the polymerisation vessel was about the same (120 c.c.) each time.

During polymerisation, carried out in a thermostat at 65° ± 0·07°, the viscometer was removed at known intervals, the reaction arrested by chilling, and measurements were taken at 25°. On reimmersion at 65° two minutes were allowed for the heating up, in plotting the data.

Measurements.—20—25 Minutes were allowed for the styrene to attain temperature equilibrium, with the viscometer clamped vertically through the centre of the coil (Fig. 5) by means of non-magnetic clamps. Density measurements were made as already described for the calibration of the float, the float being kept in the wide part of the viscometer tube away from the constrictions. As the viscosity of the styrene increased during polymerisation it became more and more difficult to obtain an accurate estimate of the density. This difficulty was overcome to some extent by attaching an electric buzzer to the bulb of the densitometer–viscometer. The vibration helped to overcome the friction between the float and the viscometer tube. Several readings were taken and the mean was used in the calculation of density. To measure the relative viscosity of the partly polymerised styrene, the viscometer tube was withdrawn slightly from the coil until the tail of the float slid through the constriction. This served to centre the float so that it rose freely without touching the sides when the current through the coil was switched off. The time of rise between two marks on the viscometer was noted. This operation was also repeated several times, and the mean time of rise t used to calculate the relative viscosity $\eta_r = i^2t/i_0^2t_0 = \rho_0 t/\rho t_0$.

Thanks are due to Messrs. Bakelite Ltd. for their gift of styrene.

QUEEN'S UNIVERSITY, BELFAST, N. IRELAND. [*Received, February 25th,* 1948.]

---

455. *The Strength of Heterocyclic Bases.*

By ADRIEN ALBERT, REGINALD GOLDACRE, and JOHN PHILLIPS.

The relative strength of heterocyclic bases constitutes a comparatively unexplored territory. Ionisation constants are now recorded for 120 heterocyclic bases belonging to 30 different, completely unsaturated, ring systems.

The principle of *additional ionic resonance*, which is known to be responsible for the enhanced basic strength of 2- and 5-aminoacridines, is shown to operate in many other nuclei.

The insertion of a further nitrogen into a pyridine ring (as in phenazine or quinoxaline) is shown to cause a marked lowering of basic strength, whereas the insertion of a further nitrogen into a pyrrole ring (as in indazole or benziminazole) creates definite basic properties where none was demonstrable before.

The addition of a benzene ring to a heterocyclic base, so that two carbon atoms are shared, usually affects the basic strength to only a relatively small extent.

THE strength of *saturated* heterocyclic bases is known to be approximately that of the corresponding aliphatic amines (*ca.* pK_a 10). However, little exact information is available concerning the strength of *unsaturated* heterocyclic bases. Of these, the acridine series has been most thoroughly explored and a survey of 115 acridines (Albert and Goldacre, *J.*, 1943, 454; *J.*, 1946, 706) has facilitated the prediction of approximate pK values in this series, an important consideration in chemotherapy because the kationic species is by far the most antibacterial.

The strengths of bases derived from 30 other heterocyclic systems have now been surveyed and interpreted from the following standpoint. The ionisation constants of these heterocyclic systems differ qualitatively from those of saturated systems through having a component not found in the latter. This component comes from the change (upon ionisation) in the energetics of the resonating system of π electrons, in which system the basic centre is intimately concerned. Hence the ionisation constant, as the measure of the free-energy change on ionisation, must carry a term closely related to the change in resonance energy upon adding a proton to the nitrogen. If it were possible to calculate this resonance change and to estimate the ionisation entropy change, the results reported here could be discussed in terms of fundamental thermodynamics. However, such calculations are not yet possible and hence the plan followed has been to deal with the more striking features of the new data in terms of the qualitative resonance energy ideas used in interpreting our acridine work.

The most important of these is the "additional ionic resonance effect" conveniently illustrated as follows. Acridine itself is a fairly weak base of pK_a 5·6 (cf. Table II). The strength rises slightly when an amino-group is inserted in the 3- or 4-position (normal amino-derivatives) and is distinctly weakened if this group is in the 1-position (*ortho*-effect). However, an amino-group in the 2- or 5-position adds greatly to the basic strength because it brings about a resonance in the ions [through the pairs of canonical structures (VI, *a* and *b*) and (VII, *a* and b)] additional to that provided by the non-ionised molecule (Albert and Goldacre, *loc. cit.*). The

case of 2-aminoacridine suggests that the loss of a Kekulé ring can be largely compensated for by the type of *p*-quinonoid structure shown (VII, *b*). On the other hand, an *o*-quinonoid structure, of the type of (VIII), although a possible contributor to the ion of 4-aminoacridine, is of little value for this purpose.

As this " additional ionic resonance effect " furnished the strongest aminoacridine bases, it was decided to pay particular attention to it in other heterocyclic series. Before investigating these, it was thought advisable to consider those open-chain compounds which show this effect in its simplest form.

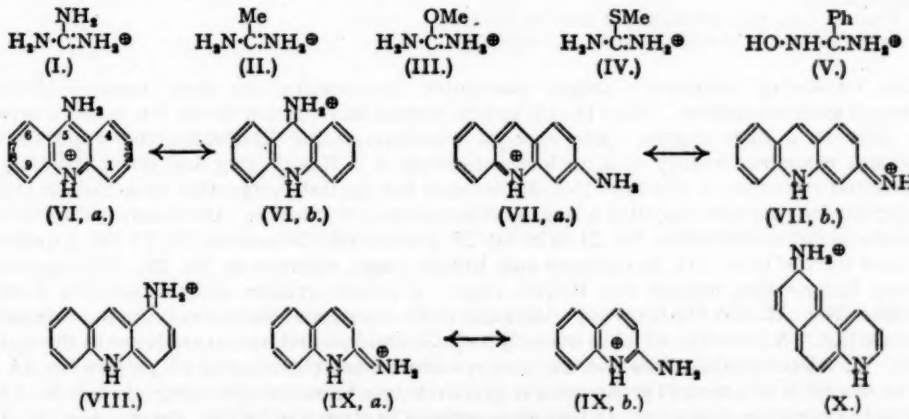
TABLE I.

Ionisation of open-chain bases having additional ionic resonance, determined in water at 20°.

No.	Substance.	pK_a.*	Dilution (1/M.).	Mode of preparation.	M. p.
1	[Guanidine (I)] †	13·71	0·5	—	—
2	Acetylguanidine	8·33	20	A	142°
3	[Phenylguanidine] ‡	10·88	30	—	—
4	[Acetamidine (II)] §	12·52	25	—	—
5	Benzamidine	11·6	10	B	80
6	[*O*-Methyl*iso*urea (III)] ‖	9·80	50	—	—
7	[*N*-Phenyl-*O*-methyl*iso*urea] ¶	7·3	—	—	—
8	*S*-Methyl*iso*thiourea (IV)	9·83	40	C	—
9	*N*-Phenyl-*S*-methyl*iso*thiourea	7·14	160	D	71
10	Benzamidoxime (V)	4·82	160	E	78

* pK_a is the negative logarithm of the acidity constant $[B][H^+]/[BH^+]$.
† Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.
‡ Davis and Elderfield, *J. Amer. Chem. Soc.*, 1932, **54**, 1499.
§ Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162.
‖ Zief and Edsall, *J. Amer. Chem. Soc.*, 1937, **59**, 2245.
¶ Bruce, *ibid.*, 1904, **26**, 419 (conductimetry).
A Korndörfer, *Arch. Pharm.*, 1903, **241**, 467.
B Pinner and Klein, *Ber.*, 1878, **11**, 6.
C The sulphate (Shildneck and Windus, *Org. Synth.*, 1932, **12**, 52) was titrated with alkali.
D Bertram, *Ber.*, 1892, **25**, 49.
E Tiemann and Kruger, *Ber.*, 1884, **17**, 1865.

It will be seen from Table I that guanidine (I) is the strongest base of the series. Its ion has three equivalent structures in which each NH_2 in turn carries the katonic charge and the double bond, making for a higher degree of resonance than exists in the non-ionised molecule and thus accounting for the extraordinarily high basic strength (cf. Pauling, " The Nature of the Chemical Bond ", Cornell, 1942, p. 213; Branch and Calvin, " The Theory of Organic Chemistry ", Prentice-Hall, 1941, p. 194). The case of acetamidine (II) is similar, but the fact that there are only two equivalent structures contributing to the ion has led to a loss of basic strength, partly compensated by the electron-donating properties of the methyl group. In *O*-methyl*iso*urea (III) and *S*-methyl*iso*thiourea (IV), the electron-donating methyl group has been replaced by



electron-attracting groups, with some loss of basic strength. Nos. 2, 3, 5, 7, and 9 were included in this comparison, to help assess the effects of electron-attracting groups on these values, which

are subject to similar influences in heterocyclic nuclei. The resultant pK_a values may be compared with those of 5-aminoacridine (9·99), which is a vinylogous amidine and 2 : 5-diaminoacridine (11·49), which is a vinylogous guanidine. We shall see that when not one, but two, hetero-atoms of these open-chain bases form part of a heterocyclic ring, cross-resonances seriously reduce the base-strengthening features of their structure [cf. acetamidine and pyrimidine (No. 79); guanidine and 2-aminopyrimidine (No. 80); *S*-methyl*iso*thiourea and 2-aminothiazole (No. 129)]. Benzamidoxime (V), the ion of which has no equivalent resonance structures and is electronegatively substituted, is seen to be a weak base.

Quinoline and Pyridine compared with Acridine.—Table II lists the pK_a values of pyridine and quinoline and all their monoamino-derivatives. Some of these values have been reported in brief (Albert and Goldacre, *Nature*, 1944, **153**, 467) but they have now been more accurately established by repeated titrations averaging 6—10 points on the curve. Acridine compounds substituted in analogous positions have been placed opposite the corresponding pyridine and quinoline compounds to facilitate comparison. The lower solubility in water of the acridines necessitated a higher dilution [see Experimental Section for the (small) effect of concentration on pK].

It may be seen from Table II that the removal of one or two benzene rings from acridine and the aminoacridines has affected most of the pK values, but not profoundly. Acridine is the strongest and quinoline the weakest of the unsubstituted bases, but the differences are small. Nos. 13, 17, 19, and 20 would be classed as normal amino-derivatives (as defined above for Nos. 27 and 28); they show a small elevation in pK_a (0·01—1·4 units). No. 22 (8-aminoquinoline) shows an *ortho*-effect (depression of pK_a) comparable to that of its acridine analogue (No. 30).

TABLE II.

The ionisation of heterocyclic bases (1 *nitrogen atom in ring*) (*determined in water at* 20°).

No.	Pyridine series.	pK_a.	Dilution (1/M.).	M. p.
11	Pyridine	5·23 *	60	—
12	2-Amino-	6·86 †	60	57°
13	3-Amino-	5·98 †	60	64
14	4-Amino-	9·17 ‡	45	158

No.	Quinoline series.	pK_a.	Dilution (1/M.).	M. p.
15	Quinoline	4·94 *	60	—
16	2-Amino-	7·34	60	131°
17	3-Amino-	4·95	60	94
18	4-Amino-	9·17	60	154
19	5-Amino-	5·46	60	110
20	6-Amino-	5·63	60	117
21	7-Amino-	6·65	60	94
22	8-Amino-	3·99	60	65
23	4-Amino-2-methyl-	9·44	240	164
24	2 : 4-Diamino-	9·45	40	197—198

No.	Acridine series.	pK_a.§	Dilution (1/M.).
25	Acridine	5·60	2500
—	(no analogue)	—	—
—	(no analogue)	—	—
26	5-Amino-	9·99	2500
27	4-Amino-	6·04	6000
28	3-Amino-	5·88	6000
29	2-Amino-	8·04	5000
30	1-Amino-	4·40	3000

* These values are in good accord with numerous other determinations in the literature.

† Tropsch, *Monatsh.*, 1914, **35**, 777, obtained 7·2 for the 2-isomeride and 6·6 for the 3-isomeride (conductimetry).

‡ Tropsch (*loc. cit.*) obtained 9·2 (conductimetry).

§ Taken from Albert and Goldacre, *J.*, 1946, 706.

The remaining compounds might reasonably be expected to show some evidence of additional ionic resonance. Nos. 14, 18, and 26 (which have an ion of the VI, *a* and *b* type) all show this to a high degree. The case of 4-aminopyridine illustrates the approximately equivalent resonance energy of a nucleus consisting of a Kekulé ring and one consisting of a *p*-quinonoid structure of the type (VI, *b*), because the partial destruction of a Kekulé ring, in forming the ion, has not cancelled a large additional ionic resonance. However, additional ionic resonance is not so marked in No. 21 as in No. 29, presumably because in No. 21 one *p*-quinonoid structure (of the type VII, *b*) replaces two Kekulé rings, whereas in No. 29, one *p*-quinonoid and one Kekulé ring replace two Kekulé rings. 2-Aminopyridine and particularly 2-aminoquinoline (Nos. 12 and 16) show an additional ionic resonance effect involving an *o*-quinonoid structure (*e.g.*, IX, *a* and *b*) which is actually a cyclic amidine and has no analogue in the acridine series. 2 : 4-Diaminoquinoline (No. 24) does not show much elevation of pK_a above No. 18.

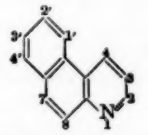
The insertion of a methyl group usually gives rise to a base-strengthening effect (0·3—1·0 pK unit) in the pyridine, quinoline, and acridine series (Constam and White, *Amer. Chem. J.*, 1903, **29**, 46; Felsing and Biggs, *J. Amer. Chem. Soc.*, 1933, **55**, 3624; Albert and Goldacre, 1946, *loc. cit.*), particularly if it is in the α- or γ-position. 4-Amino-2-methylquinoline (No. 23) is the

first of several fresh examples of this effect encountered in the present work (see also Tables III and V).

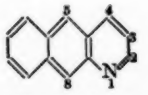
TABLE III.

The ionisation of heterocyclic bases (1 *nitrogen atom in ring*) (*continued*).

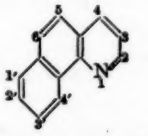
(Determined in water, except for values in parentheses which were determined in 50% alcohol, all at 20°.)



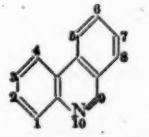
5 : 6-Benzquinoline.



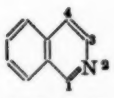
6 : 7-Benzquinoline.



7 : 8-Benzquinoline.



Phenanthridine.



*iso*Quinoline.

No.	Substance.	pK_a.	ΔpK_a, water — alcohol.	Dilution (1/M.).	Source.	M. p.
31	5 : 6-Benzquinoline	5·15 (3·90)	1·25	10,000 (40)	F	94°
32	4-Amino-	(7·99)	—	(60)	G	150—151
33	4-Amino-2-methyl-	(8·45)	—	(120)	G	161
34	2-Methyl-	(4·44)	—	(160)	I	83
35	2-Amino-4-methyl-	7·14 (6·51)	0·63	100,000 (200)	G	224—225
36	4′-Amino-	5·20 (4·10)	1·10	(40)	J	175
37	3′-Amino-	(4·02)	—	(80)	H	222—224
38	1′-Amino-	5·03	—	10,000	H	156—157
39	2′ : 4′-Diamino-	(4·91)	—	(60)	J	249
40	6 : 7-Benzquinoline	5·05 (3·84)	1·21	7,000 (120)	G	116·5
41	4-Amino-	(8·75)	—	(300)	G	233 (sealed)
42	4-Amino-2-methyl-	(9·45)	—	(160)	G	180
43	4-Amino-2-methyl-8-chloro-	(5·95)	—	(300)	G	179—180
44	8-Chloro-	(2·5)	—	(160)	K	142
45	3 : 4-Diamino-	(8·15)	—	(320)	G	212 (dec.)
46	3-Amino-	4·78 (3·73)	1·05	10,000 (400)	G	240—241
47	7 : 8-Benzquinoline	4·25 (3·15)	1·10	10,000 (40)	L	52
48	4-Amino-	(7·68)	—	(120)	G	173—174
49	4-Amino-2-methyl-	(7·96)	—	(60)	G	149—150
50	2-Amino-4-methyl-	6·74 (6·02)	0·72	20,000 (240)	G	133—134
51	6-Amino-2-methyl-	(5·23)	—	(160)	G	128—129
52	1′-Amino-2-methyl-	(4·75)	—	(160)	G	141·5
53	Phenanthridine	(3·30)	—	(60)	G	107—108
54	9-Amino-	7·31 (6·75)	0·56	13,000 (120)	M	195
55	2-Amino-9-methyl-	(5·66)	—	(160)	N	173
56	7-Amino-9-methyl-	(5·23)	—	(160)	N	232
57	2 : 7-Diamino-9-methyl-	(6·26)	—	(160)	N	265
58	2 : 7 : 9-Triamino-	(8·06)	—	(160)	G	200
59	[*iso*Quinoline]	5·14 *	—	—	—	—
60	1-Amino-	7·62	—	160	O	123

* Determined by Kolthoff, *Biochem. Z.*, 1925, **162**, 289.

F Knueppel, *Ber.*, 1896, **29**, 708.

G Albert, Brown, and Duewell, this vol., p. 1284.

H A specimen was kindly presented by Prof. C. Hamilton of the University of Nebraska.

I Eastman-Kodak, recrystallised.

J Clem and Hamilton, *J. Amer. Chem. Soc.*, 1940, **62**, 2349.

K Clemo and Driver, *J.*, 1945, 829.

L Haid, *Monatsh.*, 1906, **27**, 318.

M Morgan and Walls, *J.*, 1932, 2225.

N A specimen was kindly presented by Dr. L. Walls of the Wellcome Chemical Research Laboratories.

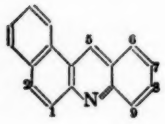
O Chichibabin and Oparina, *J. Russ. Phys. Chem. Soc.*, 1920, **50**, 543.

Benzquinolines, Phenanthridines, and Benzacridines.—Tables III and IV record the pK_a values of some representative members of 8 other heterocyclic series having one ring-nitrogen. Unfortunately, the very sparing solubility of these substances (particularly the primary amines) in water and, in some cases, the lack of a decided colour-change upon ionisation, often necessitated carrying out potentiometric titrations in aqueous alcohol. However, 12 of the compounds were examined in water (colorimetrically in a series of buffers) and if these compounds may be taken as representative, the ΔpK values (depressions of pK_a due to alcohol)

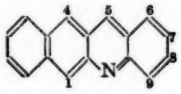
TABLE IV.

The ionisation of heterocyclic bases (1 *nitrogen atom in ring*) (*concluded*).

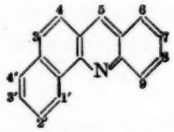
(Determined as in Table III.)



3 : 4-Benzacridine.



2 : 3-Benzacridine.



1 : 2-Benzacridine.

No.	Substance.	pK_a.	ΔpK_a, water — alcohol.	Dilution (1/M.).	Source.	M. p.
61	3 : 4-Benzacridine	4·70 (4·16)	0·54	* (160)	P	132°
62	5-Amino-	(8·41)	—	(240)	G	236—237
63	7-Amino-	(5·03)	—	(170)	G	237—238
64	8-Amino-	7·42 (6·51)	0·91	33,000 (300)	Q	264—265
65	8-Acetamido-	(4·48)	—	(320)	Q	269
66	8-Dimethylamino-	7·31 (6·99)	0·32	48,000 (240)	R	184
67	2 : 3-Benzacridine	(4·52)	—	(480)	G	223
68	5-Amino-	(9·72)	—	(120)	G	231—232
69	5-Acetamido-	(4·56)	—	(640)	G	*ca.* 230 (dec.)
70	7-Amino-	(5·38)	—	(320)	G	285—286
71	5-Amino-6 : 7 : 8 : 9-tetrahydro-	(9·66)	—	(60)	G	236—238
72	1 : 2-Benzacridine	(3·45)	—	(160)	S	108
73	5-Amino-	(8·13)	—	(320)	G	196—197
74	7-Amino-	(4·05)	—	(160)	G	165
75	8-Amino-	6·72 (5·97)	0·75	40,000 (240)	Q	200
76	4′ : 5-Diamino-	(8·44)	—	(200)	G	225—226

* The pK in water was determined by extrapolation from titrations in 50, 40, 30, and 20% alcohol to 0% alcohol.

G As in Table III.

P Baezner, *Ber.*, 1904, **37**, 3077.

Q Albert, this vol., p. 1225.

R Ullmann and Marić, *Ber.*, 1901, **34**, 4318. A sample was kindly presented by Drs. L. Small and L. Sargent through the Anti-Malarial Survey.

S Ullmann and La Torre, *Ber.*, 1904, **37**, 2922.

cover much the same range as that found in the acridine series. The nature of the connexion between the value of this depression and the molecular structure has been discussed (Albert and Goldacre, *loc. cit.*, 1946), and the extreme values known are zero (4-aminoquinoline) and 1·49 pK units (acridine) but most of them lie between 0·5 and 0·8. In any given series, the members with additional ionic resonance usually have the smallest ΔpK's.

It is seen from the tables that the parent substances (Nos. 31, 40, 47, 53, 61, 67, and 72) have pK's close to those of quinoline and pyridine. The 7 : 8-benzquinolines and 1 : 2-benzacridines, which share a structural feature, are weaker bases than their isomerides. The following are classified as normal amino-derivatives, as defined above for 3- and 4-aminoacridines, and it will be seen that the elevation of pK is of the same order as in the quinoline and acridine series (cf. Table II) : Nos. 36, 37, 38, 39, 46, 51, 52, 56, 63, 70, and 74.

An elevation of pK derived from an additional ionic resonance of the type (VI, *a*, *b*) is seen in Nos. 32, 33, 41, 42, 45, 48, 49, 62, 68, 71, 73, and 76 and is of the same size as in 4-aminoquinoline and 5-aminoacridine (*i.e.*, *ca.* 5·0 units).

Elevations of pK similarly derived from the ionic resonance (VII, *a* and *b*) occur in Nos. 64, 66, 75, and possibly 55, and are of the same size as in 2-aminoacridine. Further elevations similarly derived (from IX, *a* and *b*) are found in Nos. 35, 50, 54, 58, and 60 and are of the same size as in 2-aminoquinoline. Because phenanthridine may be regarded as benzo*iso*quinoline, the relevant *iso*quinolines (Nos. 59 and 60) have been included for comparison.

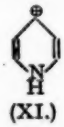
Small but definite elevations due to a methyl group appear quite consistently, as in the quinoline and acridine series and the usual examples of depression due to *N*-acetylation or *C*-chlorination were found (Nos. 65, 69, 43, and 44). No. 45, compared with No. 41, appears to show an *ortho*-effect comparable with that of *o*-phenylenediamine.

The angular series in Tables III and IV have three Kekulé rings and all the nuclear stability

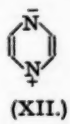
that goes with this structure. However, the formation of ions of the types (VI), (VII), and (IX) does not destroy any more Kekulé structures in the benzquinoline and benzacridine series than in the quinoline or acridine series. On the other hand, it is not expected that structures (such as X) which entirely destroy the Kekulé structure could give rise to additional ionic resonance : the low pK's of Nos. 36 and 39 support this.

Six-membered Rings with Two Nitrogen Atoms.—Reference to Table V shows that the introduction of a second nitrogen into a six-membered ring already containing a nitrogen atom greatly reduces the basic strength, often by as much as 4 pK units. Pyridine (No. 11) may be compared with pyridazine, pyrimidine, and pyrazine (Nos. 77, 79, 88), quinoline (No. 15) with cinnoline, phthalazine, quinazoline, and quinoxaline (Nos. 90, 92, 94, and 99), and acridine (No. 25) with phenazine (No. 104).

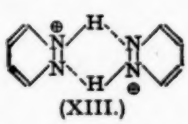
A small loss of basic strength upon the introduction of a second nitrogen is seen even in saturated compounds, *e.g.*, the pK_a of ammonia, 9·3, falls to 8·5 in hydrazine (Bredig, *Z. physikal. Chem.*, 1894, **13**, 289) and that of piperidine, 11·6, falls to 10·3 in piperazine (Kolthoff, *Biochem. Z.*, 1925, **162**, 289). However, the loss is greater in the present series because several factors are involved. In the first place, the second nitrogen atom is electron-attracting and hence base-weakening. Then, in several cases there are opportunities for the formation of *exactly equivalent* dipolar structures in the non-ionised molecule (*e.g.*, XII) and these may strengthen the resonance of this species at the expense of the ion. The particularly low pK_a values of pyrazine, quinoxaline, and phenazine (Nos. 88, 99, and 104) are cases in point. These substances are vinylogues of azobenzene, which is a very weak base for a similar reason (cf. also molecular nitrogen in this connexion). However, pyridazine, cinnoline, and phthalazine (Nos. 77, 90, and 92), which have adjacent nitrogens and hence appear more clearly to resemble azobenzene, are capable of forming hydrogen-bonded pairs of ions (*e.g.*, XIII) which have extra resonance relative to the non-ionised molecule. This is not possible in *trans*-azobenzene for steric reasons.



(XI.)



(XII.)



(XIII.)

It is of interest that cinnoline was described as a " strong base " (Busch and Rast, *Ber.*, 1897, **30**, 521) although the pK_a is now found to be only 2·70. Several other instances have come to light where a writer has been misled as to the strength of bases by relying on criteria other than an actual pK measurement.

Table V contains a few examples of normal amino-derivatives of the type of 3-aminoacridine, *viz.*, Nos. 82, 97, and 105, and, as expected, the pK is not increased by more than 2 units. No. 98 shows the *ortho*-effect, but Nos. 101 and 105 do not because in the latter both nitrogens are equivalent. The remainder of the amino-derivatives would be expected to show additional ionic resonance due to one or other of the types (VI), (VII), or (IX) discussed above. With one exception (2-aminoquinazoline, No. 95) the expected increment of over 2 pK units is found. Table V also contains some polyamino-compounds in which each amino-group separately has been shown to introduce additional ionic resonance (Nos. 85, 86, 103, 108, and 109). These compounds would bear the same relation to the corresponding monoamino-derivatives which guanidines bear to amidines were it not for the many possibilities for cross-resonances. 2 : 4-Diaminopyrimidine (No. 85) exemplifies mutual reinforcement of basic strength but 2 : 4 : 6-triaminopyrimidine (No. 86) is weaker, a curious fact which we have carefully confirmed (cf. also Nos. 106 and 109).

The usual slight base-strengthening properties of the methyl group are seen again in Nos. 87, 83, and 84, the last two examples being of interest because of the sulphonamide drugs derived from them.

The effect of inserting more than two nitrogens into a six-membered ring should, by extrapolation, be very base-weakening. Unfortunately, such compounds are unstable. Although no synthesis of 1 : 3 : 5-triazine has been recorded, two of its amino-derivatives are listed in Table VI (Nos. 110 and 111). It will be seen that they are about 1·5 units weaker than the corresponding pyrimidines (Nos. 84 and 86).

A small selection of phenanthrolines has also been included in Table VI to represent heterocyclic compounds with two nitrogens in *different* rings. The pK_a values of Nos. 112—114 are approximately equal to those of the corresponding benzacridines (Table III) and hence form a contrast to phenazine (No. 104) with which they are isomeric.

TABLE V.

The ionisation of heterocyclic bases (2 *nitrogen atoms in a six-membered ring*).

(Determined as in Table III.)

No.	Substance.	pK_a.	Dilution (1/M.).	Source.	M. p.	B. p.
77	Pyridazine	2·33	10	T	—	205—206°/760 mm.
78	[3-Amino-]	5·19 *	—	—	—	—
79	Pyrimidine	1·30	15	U	—	123/760 mm.
80	2-Amino-	3·54	10	V	127—128°	—
81	4-Amino-	5·71	200	W	151—152	—
82	[5-Amino-]	2·83 *	—	—	—	—
83	2-Amino-4-methyl-	4·15	60	X	159—160	—
84	2-Amino-4 : 6-dimethyl-	4·85	160	X	153	—
85	2 : 4-Diamino-	7·26	160	W	144—145	—
86	2 : 4 : 6-Triamino-	6·84	160	Y	245—246	—
87	4-Methyl-	1·98	20	U	—	—
88	Pyrazine	0·6	10	Z	—	118/760 mm.
89	2-Amino-	3·14	20	AA	117—119	—
90	Cinnoline	2·70	150	BB	37—38	—
91	4-Amino-	6·84	160	CC	210	—
92	Phthalazine	3·47	80	DD	91—92	—
93	1-Amino-	6·60	150	EE	210—211	—
94	Quinazoline	3·51 (3·2) †	15 (50) (27°)	FF	—	241/760 mm.; 133/23 mm.
95	2-Amino-	4·43	150	GG	206	—
96	4-Amino-	5·73	150	GG	272	—
97	[6-Amino-]	(3·2) †	(50) (27°)	—	—	—
98	[8-Amino-]	(2·4) †	(50) (27°)	—	—	—
99	Quinoxaline	~0·8	10	HH	28	228—229/760 mm.
100	2-Amino-	3·96	150	II	155—156	—
101	5-Amino-	2·62	150	JJ	94—95	—
102	6-Amino-	2·95	160	KK	158—159	—
103	2 : 3-Diamino-	4·70	240	KK	(dec.)	—
104	Phenazine ‡	1·23±0·10	3000	LL	173—174	—
105	1-Amino-	(2·6)	(300)	MM	175—176	—
106	2-Amino-	4·75 (3·46)	12,000 (120)	NN —	279 —	— —
107	1 : 3-Diamino-	(5·64)	(240)	MM	274—275	—
108	2 : 3-Diamino-	(4·74)	(130)	OO	(dec.)	—
109	2 : 7-Diamino-	4·63 (3·9)	8000 (160)	PP —	(dec.) —	—

* Unpublished value kindly communicated to us by Dr. R. O. Roblin, of The American Cyanamid Co.'s Laboratory, Stamford.

† These results are reproduced from Elderfield, Williamson, Gensler, and Kremer (*J. Org. Chem.*, 1947, **12**, 405).

‡ Phenazine proved to be photosensitive, hence its solution was prepared in the light of a 5-watt red lamp. By fairly rapid working, consecutive readings on the absorptiometer (violet glass filter) agreed well.

T Evans and Wiselogle, *J. Amer. Chem. Soc.*, 1945, **67**, 60. A specimen was kindly presented by Dr. Wiselogle.

U Gabriel and Colman, *Ber.*, 1899, **32**, 1534.

V A quantity was kindly presented by Monsanto, Ltd., and was recrystallised.

W The corresponding chloro-compound was heated with alcoholic ammonia at *ca.* 180° for 8 hours (K. F. Baker, unpublished).

X Benary, *Ber.*, 1930, **63**, 2601; Combes and Combes, *Bull. Soc. chim.*, 1892, **7**, 791. Samples were kindly presented by Prof. A. K. Macbeth of Adelaide.

Y A quantity was kindly presented by Dr. G. M. Dyson and recrystallised.

Z A quantity was kindly presented by Dr. R. O. Roblin and refractionated.

AA Ellingson, Henry, and McDonald, *J. Amer. Chem. Soc.*, 1945, **67**, 1711; Weijlard, Tishler, and Erickson, *ibid.*, p. 802.

BB Jacobs, Winstein, Henderson, and Spaeth, *ibid.*, 1946, **68**, 1310. A quantity of the hydrochloride, m. p. 160—162°, was kindly presented by Prof. Jacobs. The base was titrated immediately after fractionation.

CC Baker, this vol., p. 1713.

DD Gabriel and Müller, *Ber.*, 1895, **28**, 1830.

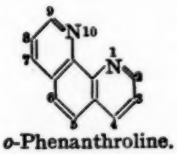
EE A specimen was kindly supplied by Prof. A. K. Macbeth and Mr. H. Rodda of Adelaide (unpublished preparation).

FF Riedel, D.R.-P., 174,941, 1905 (Friedl., **8**, 1238).
GG Macbeth and Rodda, *Nature*, 1945, **156**, 207.
HH Hinsberg, *Ber.*, 1884, **17**, 318.
II Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1944, **66**, 1957.
JJ Platt and Sharp, *J.*, in the press.
KK Specimens were kindly presented by Merck & Co., Inc., Rahway, recrystallised and analysed.
LL Kehrman and Havas, *Ber.*, 1913, **46**, 342.
MM Albert and Duewell, *J. Soc. Chem. Ind.*, 1947, **66**, 11.
NN Wohl and Lange, *Ber.*, 1910, **43**, 2187.
OO Fischer and Hepp, *Ber.*, 1889, **22**, 356 (analysed).
PP D.R.-P. 148,113, 1902 (Friedl., **7**, 341). A specimen was kindly presented by Dr. W. M. Clark through the Anti-Malarial Survey (analysed).

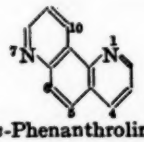
TABLE VI.

Ionisation of heterocyclic bases (*3 nitrogen atoms in a six-membered ring; or 1 nitrogen atom in each of two six-membered rings*).

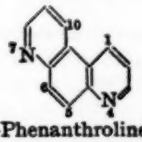
(Determined as in Table III.)



o-Phenanthroline.



m-Phenanthroline.



p-Phenanthroline.

No.	Substance.	pK_a.	Dilution (1/M.).	Source.	M. p.
110	2-Amino-4 : 6-dimethyl-1 : 3 : 5-triazine	3·60	60	QQ	171—172°
111	Melamine (2 : 4 : 6-triamino-1 : 3 : 5-triazine)	5·16 *	160	RR	—
112	*o*-Phenanthroline	(4·27)	(40)	SS	117 (anhydrous)
113	*m*-Phenanthroline	(3·11)	(40)	TT	78
114	*p*-Phenanthroline	(3·12)	(40)	TT	177
115	1-Amino-	*ca.* 7·3 (7·29)	110 (320)	G	204
116	1 : 10-Diamino-3 : 8-dimethyl-	(8·76 & 6·31)	(160)	UU	324 (dec.)
117	2 : 2′-Dipyridyl	4·23	160	VV	69

* This compares with the values, 5·1 (spectroscopy) and 5·0 (titration), obtained by Dixon, Woodberry, and Costa, *J. Amer. Chem. Soc.*, 1947, **69**, 599.

QQ Tscherven-Iwanow, *J. pr. Chem.*, 1892, **46**, 147.
RR A specimen, kindly presented by Dr. C. Gibian of Timbrol, Ltd., Sydney, was recrystallised and analysed (C, H, and N).
SS G. F. Smith Chemical Co., Columbus, Ohio, recrystallised.
TT Specimens, kindly presented by Prof. W. O. Kermack, were recrystallised.
UU Jacini, *Gazzetta*, 1939, **69**, 111; 1940, **70**, 621.
VV British Drug Houses, recrystallised.

The increased basic strength of *o*-phenanthroline, compared with its isomerides, is ascribed to the simultaneous union of one proton to both nitrogens (by electrovalent and hydrogen bonds, respectively). This effect is not evident in the somewhat similarly constituted 2 : 2′-dipyridyl (No. 117) doubtless because of its free rotation around the 2 : 2′-bond.

1-Amino-*p*-phenanthroline (No. 115) does not give a titration curve of theoretical slope in water, in which it forms a somewhat viscous solution. An ion–base association, stronger than those described in the acridine series (Albert and Goldacre, *loc. cit.*, 1946), is indicated. The conditions are favourable because, in the mono-ion, one ring nitrogen will carry a formal negative charge and the other an ionic positive charge. The titration curve in 50% alcohol is almost regular. No. 116 is an interesting case of two (almost) independent additional ionic resonances in the one molecule (contrast 2 : 5-diaminoacridine, Albert and Goldacre, *loc. cit.*).

Heterocyclic Five-membered Rings.—Five-membered rings containing only one nitrogen are well known to be weak bases; for example, the pK_a of 0·4 has been calculated for pyrrole (Hall, *J. Amer. Chem. Soc.*, 1930, **52**, 5123), and indole is apparently no stronger. It is generally agreed (cf. Sidgwick, " Organic Chemistry of Nitrogen ", Oxford 1937, p. 490) that this effect is ascribable to a base-weakening resonance in which the nitrogen of the non-ionised molecule becomes positive and quaternary, somewhat as in aniline.

It has been known for some time that in at least three cases (pyrazole, glyoxaline, and

TABLE VII.

The ionisation of heterocyclic bases (five-membered rings).

(Determined as in Table III.)

No.	Substance.	Basic pK_a.	Dilution (1/M.).	Source.	M. p.	Acidic pK_a.
(a) *Two nitrogens in ring*						
118	[Pyrazole]	2·53 *	—	—	—	—
119	[Glyoxaline]	7·03 †	10 to 100	—	—	—
120	Indazole	1·3±0·2	100	WW	147—148°	—
121	3-Amino-	3·15	100	XX	154	—
122	6-Amino-	(3·66)	(160)	WW	206	—
123	Benziminazole	5·53 ‡	40	YY	170	12·3
124	2-Amino-	7·54	160	VV	222	—
(b) *More than two nitrogens in ring*						
125	[1 : 2 : 4-Triazole]	2·55 *	—	—	—	—
126	Benztriazole	1·6	20	ZZ	99	8·57 §
127	5-Aminotetrazole	6·03 ‖	80	AAA	200	1·80
		(6·77)	(160)	—	—	(2·55)
(c) *Two different hetero-atoms*						
128	Thiazole	2·53	10	BBB	(b. p. 117)	—
129	2-Amino-	5·39	130	V	90	—
130	Benzthiazole	(1·2±0·1)	(10)	CCC	(b. p. 231/760 mm.)	—
131	2-Amino-	4·51	160	DDD	129	—
132	Benzoxazole	(decomp.)	160	EEE	(b. p. 93/18 mm.)	—
133	2-Amino-	3·73	100	DDD	130	—

* Dedichen, *Ber.*, 1906, **39**, 183 (rate of hydrolysis of ethyl formate).
† Kirby and Neuberger, *Biochem. J.*, 1938, **32**, 1146 (potentiometry).
‡ Schwarzenbach and Lutz (*Helv. Chim. Acta*, 1940, **23**, 1162) obtained 5·60 (potentiometry).
§ Schwarzenbach and Lutz, *loc. cit.*, obtained pK_a 8·44.
‖ Baur (*Z. physikal. Chem.*, 1897, **23**, 411) obtained pK_a 6·21 (conductimetry).

WW Noelting, *Ber.*, 1904, **37**, 2584. The published m. p. of 210° (Witt, Noelting, and Grandmougin, *Ber.*, 1890, **23**, 3635; Kwartler and Lucas, *loc. cit.*) appears to be corrected because 206° was the highest m. p. obtainable in spite of repeated recrystallisation with change of solvents. 6-Nitroindazole was also reduced in turn with hydrogen and Raney nickel (Kwartler and Lucas, *loc. cit.*), ammonium bisulphide (Witt *et al.*, *loc. cit.*), and tin and hydrochloric acid (Gabriel and Stelzner, *Ber.*, 1896, **29**, 307), always with the same result (Found: C, 62·8 H, 5·3; N, 31·5. Calc. for $C_7H_7N_3$: C, 63·1; H, 5·3; N, 31·6%).
XX Kwartler and Lucas, *J. Amer. Chem. Soc.*, 1943, **65**, 1804.
YY Wagner and Millett, *Org. Synth.*, 1939, **19**, 12.
ZZ Ladenburg, *Ber.*, 1876, **9**, 222.
AAA Thiele, *Annalen*, 1892, **270**, 45.
BBB McLean and Muir, *J.*, 1942, 383.
CCC Mills, *J.*, 1922, **121**, 460.
DDD Skraup, *Annalen*, 1919, **419**, 66.
EEE von Niementowski, *Ber.*, 1897, **30**, 3064.

benziminazole, Nos. 118, 119, and 123; Table VII) the insertion of another nitrogen in the ring is base-strengthening, and this has now been shown to be so for indazole also (No. 120). The base-strengthening effect of the second nitrogen, an effect which contrasts so sharply with what has been demonstrated in six-membered rings (Table V), must be ascribed to additional resonance (*e.g.*, between XIV, *a* and *b*) in the ions of each of the four compounds. From this, a base-weakening effect must be subtracted in those compounds which have adjacent nitrogens (Nos. 118 and 120) owing to hydrogen bonding of the non-ionised molecules (*e.g.*, XV; cf. Hunter, *J.*, 1941, 1). Additional ionic resonance effects, corresponding to 2-aminoquinoline, are demonstrated in some amino-derivatives (Nos. 121 and 124 and, possibly, 122). It is interesting to see 6-aminoindazole described in the literature as a strong base (Witt, Noelting, and Grandmougin, *Ber.*, 1890, **23**, 3635).

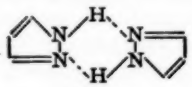
The effect of three nitrogens in a five-membered ring is shown in 1 : 2 : 4-triazole (No. 125) and benztriazole (No. 126); the base-weakening effect of the third nitrogen can be large [*e.g.*, $\Delta pK = -4{\cdot}4$ in passing from glyoxaline (No. 119) to 1 : 2 : 4-triazole].

5-Aminotetrazole is strongly acid to litmus (the pH of an M/80-solution is 4·1). It appears to be zwitterionic in nature, using the criterion afforded by titration both in alcohol and in water, *i.e.*, a rise in both pK_a values in 50% alcohol (cf. Albert and Goldacre, *loc. cit.*, 1946). The fact that the loss of a proton would make all nitrogens equivalent brings about a strong additional

resonance in the anion, hence the acidic pK is low. The electron-repelling effect of a stable anion acts as a further base-strengthening factor here.

(XIV, *a*.)

(XIV, *b*.)


(XV.)

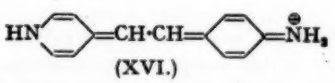

(XVI.)

Table VII concludes with a few five-membered ring systems containing two hetero-atoms. Benzoxazole was found to be decomposed to 2-formamidophenol too rapidly by acid to give a reliable titration figure. Thiazole and benzthiazole are seen to be much weaker bases than pyridine and quinoline. Additional ionic resonance is demonstrated for their amino-derivatives (Nos. 129 and 131) which are cyclic *iso*thioureas.

The following order of (increasing) basic strength was predicted by Brooker, Sprague, and Cressman (*J. Amer. Chem. Soc.*, 1945, **67**, 1889) for several compounds which have now been measured: indole, benzthiazole, quinoline, thiazole, 5 : 6-benzquinoline, pyridine, and benziminazole. These authors used an indirect, qualitative method (comparing the spectra of cyanine dyes of which these substances were constituents), but it will be seen from Tables II—VII that thiazole was not correctly placed.

Effect of adding a Benzene Ring.—The foregoing tables contain a number of examples of substances differing from one another by a benzene ring, added in such a way that two carbons are shared by two rings. This has not produced any dramatic change in pK values which have, in general, shifted by only $\pm 0{\cdot}5$—1 pK unit. The extreme examples of this effect are pyrimidine to quinazoline ($+2{\cdot}2$) and glyoxaline to benziminazole ($-1{\cdot}5$ pK unit).

Styryl Derivatives.—Some styryl compounds were examined for signs of a base-strengthening resonance derived from possible contributions to the ion of a structure such as (XVI). This seemed a remote possibility because it implied the loss of two Kekulé rings; moreover, the corresponding aminostyryl-acridines had proved to be weak bases (Albert and Goldacre, *loc. cit.*, 1943). Actually, the pK_a values of 4-(*p*-aminostyryl)- and 2 : 6-bis-(*p*-aminostyryl)-pyridine (Royer, *J.*, 1947, 560) were found to be 6·25 and 5·97 respectively (M/100,000; H_2O) and, as expected, these show little enhancement above the value for pyridine (5·23).

Experimental.

Potentiometric titration was used to obtain those pK values where the concentration is shown as M/500 or greater; in other cases absorptiometry in buffers of a series of pH values was used. Both techniques were carried out exactly as previously described (Albert and Goldacre, *loc. cit.*, 1946).

In this work the policy has been followed of carrying out potentiometric titrations at concentrations as high as solubility permitted in order to keep the hydrolysis corrections low. The effect of the various dilutions on the "classical" pK_a values, as determined, can be eliminated by transforming them into thermodynamic pK_a values by adding the following corrections, M/10, 0·23; M/50, 0·10; M/200, 0·05; M/600, 0·03.

The authors wish to thank Prof. J. C. Earl for encouraging these studies, Mr. K. F. Baker for preparing many of the compounds in Tables V and VII, and Mr. D. P. Craig for most helpful discussions. This work was supported by the National Health and Medical Research Council and the Wellcome Foundation.

University of Sydney. [*Received, February 26th*, 1948.]

---

456. *The Catechins of Green Tea. Part II.*

By A. E. Bradfield and (Miss) M. Penney.

In continuation of previous work (Bradfield, Penney, and Wright, *J.*, 1947, 32), (−)-*epi*catechin, (−)-*epi*catechin gallate, (−)-*gallocatechin gallate*, and a *substance*, which on tannase hydrolysis yields gallic acid and a new *gallocatechin*, have been isolated from green tea.

In Part I (Bradfield, Penney, and Wright, *loc. cit.*) a method was described of separating the ether-soluble polyphenols of green tea into three fractions—(*a*), (*b*), and (*c*)—by partition chromatography. Fraction (*c*) was identified as (−)-gallocatechin, while fraction (*b*) is probably (±)-gallocatechin [or (±)-*epi*gallocatechin]. Fraction (*a*) is a mixture of substances. By rechromatographing fraction (*a*) on a series of columns, using ether and a mixture of ethyl acetate and carbon tetrachloride as solvents, four main fractions—(2), (2*a*), (3), and (4)—are obtained. These appear homogeneous when again chromatographed with ether or ethyl

acetate–carbon tetrachloride, and from them crystalline substances, referred to in the following as " substance (2) " etc., are obtained. An additional substance, (2*X*), which has not yet been obtained crystalline, and traces of several other constituents have also been isolated.

Substance (2) is (−)-*epi*catechin gallate, first isolated from Japanese green tea by Tsujimura (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1930, **14**, 63; 1931, **15**, 155; 1935, **26**, 186). It has now been shown that on hydrolysis by tannase it yields gallic acid and (−)-*epi*catechin, the identity of the latter being established by direct comparison of the Debye–Scherrer diagrams given by its acetyl derivative with that of the acetate of authentic (−)-*epi*catechin from the heartwood of *Acacia catechu*. This confirms the constitution assigned to the substance by Tsujimura.

Substance (2*X*), present in relatively small amounts, gives with aqueous ferric sulphate solution a bright green colour which changes to dirty green and finally to yellow. With aqueous sodium cyanide it gives a very faint pink colour, which slowly deepens to orange, without showing any signs of fading. These colour tests indicate that the substance is a catechol derivative.*

Substance (2a) crystallises from water as minute needles or laths having $[\alpha]_D^{22^\circ}$ −46° in acetone. It yields an amorphous acetyl derivative. The presence of a pyrogallol grouping is indicated by the deep blue colour given by aqueous ferric sulphate, the colour rapidly fading to pale blue-grey, and also by the immediate pinkish-orange colour produced by sodium cyanide, which fades on standing and is restored by shaking the solution. A phloroglucinol nucleus is indicated by the vanillin test. Hydrolysis with tannase yields gallic acid and a substance (2*b*), which crystallises from water as minute needles, decomp. 200—205°, $[\alpha]_D$ ±0·0°. The colour tests given by the substance with ferric salt, sodium cyanide, and vanillin are similar to those given by the original material (2*a*). Acetylation of (2*b*) yields an *acetyl* derivative $C_{27}H_{26}O_{13}$, m. p. 140—142°. This hydrolysis product thus appears to be one of the stereoisomeric forms of gallocatechin, which is either optically inactive or of very low rotation, differing not only from (−)-gallocatechin and (±)-gallocatechin (Part I), but also from the gallocatechin isolated by Osima (*Bull. Agric. Chem. Soc. Japan*, 1939, **15**, 636) from the bark of *Casuarina equisetifolia*. It follows that substance (2*a*) is a galloyl derivative of a new gallocatechin.

The properties of substance (3) correspond with those of a substance first isolated by Tsujimura (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1929, **10**, 253) from Japanese green tea, which, from a study of its degradation reactions, she concluded to be (−)-*epi*catechin. Comparison of the Debye–Scherrer photographs of the acetate of substance (3) from tea with the acetate of (−)-*epi*catechin from *Acacia catechu* establishes the identity of the two substances.

Substance (4) crystallises from water as colourless needles, decomp. 215—216°, $[\alpha]_D^{18^\circ}$ −179°. With aqueous ferric sulphate it gives a violet-blue colour, which fades to nearly colourless in one or two minutes. With aqueous sodium cyanide an immediate pinkish-orange is obtained, which fades and is restored by shaking, and with vanillin an orange colour, soon changing to ruby red and then to magenta. The presence of pyrogallol and phloroglucinol groups is indicated. The substance has been acetylated under a variety of conditions, but the product was always a white amorphous powder which could not be induced to crystallise. With diazomethane an amorphous product was obtained, from which no crystalline fraction could be isolated. On hydrolysis of substance (4) by tannase, gallic acid and (−)-gallocatechin are obtained, both these substances and their acetates being positively identified by comparison of their Debye–Scherrer photographs with authentic specimens. Neither substance (4), nor the galloyl ester, substance (2*a*), gave entirely satisfactory carbon or hydrogen analyses, but molecular weight determinations by Barger's isopiestic method (*J.*, 1904, **85**, 286) showed both substances to be monogalloyl esters. In neither case is there, at present, any evidence to show with which hydroxyl group of the gallocatechin moiety the gallic acid is combined.

From an aqueous infusion of a Ceylon green tea, yields of the various catechins, as percentages of the total extractable polyphenols, were: (−)-gallocatechin, 11·7; (±)-gallocatechin, 5·8; (−)-*epi*catechin, 3·2; substance (2*X*), 1·2; (−)-gallocatechin gallate, 36·0; substance (2*a*), 4·7, (−)-*epi*catechin gallate, 7·5. Results closely similar have been obtained by examination of another specimen of Ceylon green tea, a China (Young Hyson) green tea, and specimens of dried leaf from Ceylon and Assam.

* *Note added April 23rd*, 1948.—Substance (2*X*) has now been obtained from water as minute needles, which on heating appear to lose water of crystallisation at ~100—110°. Slight decomposition begins at 200° and becomes vigorous at 210—215°. The optical rotation is very low or zero. The acetyl derivative crystallises from aqueous acetic acid as white needles, m. p. 164—165° (Found: C, 59·9; H, 5·10. Calc. for $C_{31}H_{24}O_{11}$: C, 60·0; H, 4·83%). These properties and those recorded above agree with the properties of (±)-catechin, a usual concomitant of (−)-*epi*catechin in plant material (Freudenberg, " Tannin, Cellulose, Lignin ", Berlin, 1933).

It has already been pointed out (Bradfield, *Chem. and Ind.*, 1946, 242) that the rather scanty evidence available suggests some resemblance in regard to their polyphenol content between tea leaf and such widely differing leaves as those of oak and chestnut. This resemblance has been heightened by the discovery, according to a recent abstract, of ellagic acid in tea (Tsujimura, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1941, **38**, 487; *Chem. Abs.*, 1947, **41**, 5924).

Light Absorption.—The tea catechins all absorb in the ultra-violet, showing a band at 270—280 mμ; the band for (−)-gallocatechin gallate is bifurcated, with twin peaks at $\lambda_{max.}$ 275 mμ and 279·5 mμ. In addition, in all cases very strong absorption takes place below about 240 mμ. Data for tea catechins and some related simpler substances in alcohol solution are given in Table I.

TABLE I.

		$\varepsilon_{max.}$	$\lambda_{max.}$			$\varepsilon_{max.}$	$\lambda_{max.}$
(*a*)	* Catechol	2600	278	(*f*)	(−)-Gallocatechin	1,340	271
(*b*)	† Pyrogallol	800	266	(*g*)	(±)-Gallocatechin	1,290	271
(*c*)	‡ Gallic acid	7900	272	(*h*)	(−)-*epi*Catechin gallate	13,600	280
(*d*)	* 5 : 7-Dihydroxy-2 : 2-dimethylchroman	624	272	(*i*)	(−)-Gallocatechin gallate	9,500 9,250	275 279·5
(*e*)	(−)-*epi*Catechin	3300	280	(*j*)	Substance (2*a*)	13,600	276

* Morton and Sawires, *J.*, 1940, 1052.

† Goslawski and Marchlewski, *Bull. Acad. Polonaise*, 1931, *A*, 383.

‡ Hertzowna and Marchlewski, *ibid.*, 1934, *A*, 55, give $\varepsilon_{max.}$ 7600, $\lambda_{max.}$ 265 mμ for the aqueous solution.

The catechin molecule may be considered to consist of two chromophores, the phloroglucinol and the catechol (or pyrogallol) nuclei, acting practically independently, and since these nuclei all absorb in the same region of the spectrum, the values of $\varepsilon_{max.}$ 3300 for *epi*catechin and $\varepsilon_{max.}$ 1340 for gallocatechin correspond approximately with the sum of the values of $\varepsilon_{max.}$ for 5 : 7-dihydroxy-2 : 2-dimethylchroman and catechol or pyrogallol respectively ($a + d = 3224$; $b + d = 1424$). The spectra of the acetyl derivatives are very similar to those of the parent catechins. The galloyl catechins show much higher values of $\varepsilon_{max.}$, a result to be expected from the introduction of a powerful chromophore. The values of $\varepsilon_{max.}$ 9500 and 9250 for the twin peaks of gallocatechin gallate are very close to the sum of the values for the three chromophores in the molecule ($b + c + d = 9324$). Acetylation of gallic acid results in the virtual disappearance of the band at $\lambda_{max.}$ 272 mμ, only a point of inflexion remaining, with ε at this point decreased to 730. Correspondingly, the amorphous acetyl derivative of (−)-gallocatechin gallate shows only a point of inflexion at λ 270 mμ, with ε decreased to 3000, the decrease being approximately equal to that resulting from acetylation of gallic acid.

For (−)-*epi*catechin gallate, on the other hand, a single peak only is observed, at $\lambda_{max.}$ 280 mμ. The value of the extinction coefficient depends on dilution, $\varepsilon_{max.}$ 11,600 at a concentration of $1{\cdot}47 \times 10^{-4}$ g./l. rising to $\varepsilon_{max.}$ 13,600 at half this concentration. In the presence of approximately 10^{-3} M-hydrochloric acid, the latter value is reduced to $\varepsilon_{max.}$ 12,200, suggesting that the anomaly is due to dissociation of the phenolic hydroxyl groups. The value of $\varepsilon_{max.}$ obtained by summing the tabulated values for *a*, *c*, and *d* is 11,124. It is rather surprising to find that the absorption spectrum for substance (2*a*) consists of a single peak with $\varepsilon_{max.}$ 13,600, $\lambda_{max.}$ 276 mμ, and thus resembles the spectrum of (−)-*epi*catechin gallate rather than that of (−)-gallocatechin gallate. Explanation of this anomaly must await more complete knowledge of substance (2*a*).

EXPERIMENTAL.

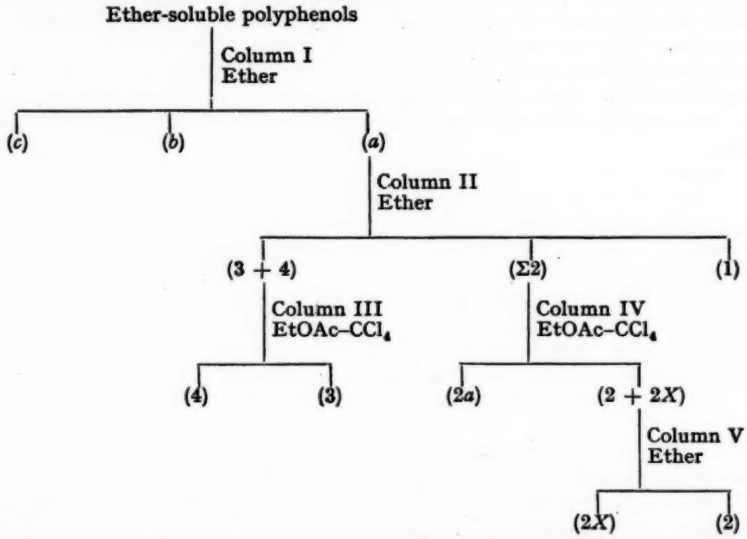
(Microanalyses are by Drs. Weiler and Strauss, Oxford.)

Preparation of Silica Gel.—For the preparation of silica gel as described in Part I, water-glass sold by Messrs. Jos. Crosfield as "special adhesive No. 2" is employed. With other commercial types of water-glass the method is not always applicable.

The presence of very fine particles in the purified gel retards the flow of solvent through a column prepared from the gel to an undesirable extent. Removal of a fine fraction by sifting (*e.g.*, with a 325-mesh sieve) is possible, but in practice clogging of the sieve is rather a handicap. We find sedimentation from water to be more convenient and more effective. For example, 100 g. of the purified silica, passing a 120-mesh sieve, is well stirred in a large beaker with 1300 c.c. of water. After the suspension has remained undisturbed for 5 minutes, the fluid portion is decanted into another beaker, and the residue filtered and dried (50 g.). After a further 30 minutes, decantation of the suspension yields a second sediment (35 g.). The first, coarser, sediment when used for a column permits very rapid passage of the solvent without noticeable loss of efficiency. With the second sediment rather lower rates are obtained, and the two materials can be mixed in suitable proportions to secure a desired rate. Using this sedimented silica, it is possible, because of the greater rate of flow, to effect two, three or four similar separations on one column within a working period of 8—10 hours, fresh portions of solution being placed on the column at such times that the first fraction from the new portion reaches the end of the column at a

convenient distance behind the last fraction of the previous portion of the solution. This practice of multiple addition results in a considerable saving of time and labour.

Chromatographic Procedure.—The complete scheme for the separation of the tea catechins is shown below, the solvent used in each case being indicated.



In general the apparatus and procedure were similar to those described in Part I, where details of Column I are given. The main data relating to Columns II—V are shown in Table II. In each case, (1) the tube used had an internal diameter of 3·1—3·3 cm., (2) the silica was mixed with 65% of its weight of water, (3) the developing solvent was the same as that used for making the solution. The ethyl acetate–carbon tetrachloride solvent used for columns III and IV was a mixture of these liquids in the proportions of 2 : 1 by volume (d 1·121), saturated with water immediately before use. In using this solvent, the rubber bung at the top of the column was replaced by a waxed cork. The products were isolated by removal of the solvent mixture under reduced pressure in a carbon dioxide atmosphere, and washed out of the flask with ether, which was then evaporated at a low temperature. The recovered solvent was washed, dried, distilled, adjusted to the correct density, and saturated with water for further use.

The position of the bands is indicated in Table II by the approximate values of R_1 and R_2 corresponding to the leading and rear edges respectively. These values vary somewhat for different specimens of silica, and depend to some extent on the relative amounts of the fractions. Although this is not shown by the approximate values of R given, the conditions are such that a small gap occurs between the fractions. In the case of column II, several narrow bands immediately precede fraction (2), the last one overlapping it slightly. These bands arise from traces of green and yellow pigments, gallic acid and of two phenolic substances.

TABLE II.

Column no.	Wt. of silica (g.).	Solution.	Fractions obtained.	R_1.	R_2.
II	70	0·5 G. fract. (*a*) in 10 c.c. ether	2	0·75	0·45
			(3 + 4)	0·45	0·26
III	50	0·25 G. fract. (3 + 4) in 5 c.c. EtOAc–CCl_4	3	0·58	0·47
			4	0·42	0·27
IV	70	0·2 G. fract. (Σ2) in 5 c.c. EtOAc–CCl_4	(2 + 2X)	0·85	0·55
			2*a*	0·55	0·35
V	70	0·25 G. fract. (2 + 2X) in 5 c.c. ether	2	0·77	0·55
			2X	0·55	0·47

(−)-epi*Catechin Gallate.*—Substance (2) (0·5 g.) crystallised from water (10 c.c.) as colourless needles, decomp. 252—254°, $[\alpha]_D^{21°}$ −190° (*c*, 0·25, in alcohol) (Found: C, 59·8; H, 4·40. Calc. for $C_{22}H_{18}O_{10}$: C, 59·7; H, 4·10%). With ferric salt the aqueous solution gave a blue colour. No immediate colour was given on addition of aqueous sodium cyanide, but a yellow-orange colour which slowly developed did not fade. With vanillin–hydrochloric acid a red to magenta colour developed. The acetyl derivative crystallised from dilute acetic acid as silky white needles, m. p. 119·5—120·5°, $[\alpha]_D^{25°}$ −96° (*c*, 0·56 in benzene). The properties correspond to those given by Tsujimura (*locc. cit.*) for (−)-*epi*-catechin gallate.

Action of Tannase on (−)-epi*Catechin Gallate.*—To a tannase solution prepared by rubbing up the dried mycelium (0·2 g.) of *Aspergillus niger* with water (9 c.c.) was added a solution of substance (2) (0·1 g.). The solution, covered with toluene, was kept at 30° for 10 days. The products were isolated by continuous extraction with ether for 72 hours, and the ether solution concentrated and chromatographed

(silica gel, 70 g.; water, 45·5 c.c.) with ether as developing solvent. Two bands corresponding to the passage of 255—322 c.c. and 515—663 c.c., respectively, of solvent through the column were obtained. From the first fraction, gallic acid, decomp. 245° (29 mg.), was obtained on evaporation. The product from the second band (40 mg.) yielded an acetyl compound, white needles, m. p. 151·5—152·5°, both alone and mixed with an authentic specimen of (−)-*epi*catechin acetate prepared from the heartwood of *Acacia catechu* by the method of Freudenberg and Purrman (*Annalen*, 1924, **437**, 274). The identity of the two acetyl compounds was confirmed by comparison of their *X*-ray diagrams.

Substance (2a).—The *substance* (0·15 g.) crystallised from water (0·2 c.c.) as minute needles, decomp. 217—219°, $[\alpha]_D^{23°}$ −46° (*c*, 0·43 in acetone) [Found: C, 56·6; H, 4·42; *M*, 436 (acetone), 431 (methyl ethyl ketone). $C_{22}H_{18}O_{11}$ requires C, 57·6; H, 3·96%; *M*, 458]. The acetyl derivative could not be obtained crystalline.

Action of Tannase on Substance (2a).—A solution of substance (2*a*) (0·15 g.) in water (2 c.c.) was treated with a solution prepared from dried mycelium of *A. niger* (0·3 g.) and kept at 30° for 14 days. The products, after extraction with ether, were chromatographed (silica, 40 g., water, 26 c.c.), and yielded two bands corresponding to the passage of 119—209 c.c. and 642—876 c.c. of solvent respectively. From the first of these fractions gallic acid was isolated (32·5 mg.) and from the second, substance (2*b*) (53 mg.), which crystallised from water as minute needles, decomp. 200—205°, $[\alpha]_D$ ±0·0° (*c*, 0·9 in alcohol). It yielded an *acetyl* derivative, m. p. 140—142° (Found: C, 58·2; H, 5·17. $C_{37}H_{34}O_{19}$ requires C, 58·1; H, 4·69%).

(−)-epi*Catechin*.—Substance (3) crystallised from water in rectangular tablets, decomp. 236—237°, and yielded an acetyl derivative, m. p. 151—152·5°, both alone and mixed with authentic (−)-*epi*catechin acetate. The identity of the two acetates was further confirmed by the *X*-ray method.

(−)-*Gallocatechin Gallate*.—*Substance* (4) (0·19 g.) crystallised from water (0·6 c.c.) as white needles which very readily became brown on exposure to air and light, decomp. 215—216°, $[\alpha]_D^{24°}$ −179° (*c*, 0·28 in alcohol) [Found: C, 56·9; H, 4·55; *M*, 443 (acetone), 437 (methyl ethyl ketone). $C_{22}H_{18}O_{11}$ requires C, 57·6; H, 3·96%; *M*, 458]. Acetylation and methylation products could not be obtained crystalline.

Action of Tannase on (−)-*Gallocatechin Gallate*.—To substance (4) (0·4 g.) in water (4 c.c.) was added a tannase solution from dried mycelium of *A. niger* (0·4 g.) and water (15 c.c.) and a few drops of toluene. After being kept at 30° for 7 days, the solution was extracted with ether, and the ether solution concentrated and chromatographed on a column prepared from silica (40 g.) and water (26 c.c.). Two bands only were observed, corresponding to the passage of 111—206 c.c., and 1232—1929 c.c., respectively, of ether through the column. From the first of these fractions gallic acid (0·115 g.), decomp. 245° (triacetate, m. p. 168—169°, both alone and mixed with an authentic specimen), was isolated. The substance (0·16 g.) isolated from the second fraction crystallised from water, decomp. 212—215°, and yielded an acetyl derivative, m. p. 191—193°, both alone and mixed with authentic (−)-gallocatechin hexa-acetate. The identity of both hydrolysis products was conclusively established by the *X*-ray method.

Molecular Weights.—Barger's method (*loc. cit.*) was followed, except that longer slugs (0·3—1·0 cm.) of the solutions were used, and measurements made with a travelling microscope. The liquid was introduced into the capillary by connecting it by means of narrow rubber tubing to the upper end of an apparatus constructed as follows. To the lower end of a thick-walled glass tube (30 cm. long, 0·2 cm. internal diameter), held vertically, a 3-inch length of rubber tubing, closed by a piece of glass rod, was attached. By pressure from a screw clip, water contained in the rubber tube was forced into the glass tube, and by subsequent manipulation of the screw clip, slugs of the required solutions could be easily drawn into, and moved up, the attached capillary. Solutions of pyrogallol were used as reference solutions. Final readings were taken with acetone as solvent after 15—18 hours, with methyl ethyl ketone after 18—40 hours.

Debye–Scherrer Photographs.—Powdered specimens of gallic acid, its acetyl derivative, and (−)-*epi*catechin acetate were made into solid cylinders (~0·3 mm. diameter) with gum tragacanth and water, and photographed by the procedure described in Part I, except that the specimens were not rotated. The remaining specimens were mounted in Lindemann glass and Perspex capillary tubes (~0·25 mm. internal diameter), and photographed using copper-$K\alpha$ nickel-filtered radiation (λ = 1·539 *kX*) from an *X*-ray tube operated at 40 ma. and 32 kv., the specimens being rotated throughout the exposures. Cylindrical cameras, 6 cm. and 9 cm. diameter, and a quarter-plate camera with a specimen-to-film distance of 5·25 cm., were used. Exposure times ranged from 2 to 16 hours. Interplanar spacings in *kX* units and relative intensities were derived as before (D = diffuse, S = strong, M = medium, W = weak, V = very, F = fairly).

Gallic acid.

7·45 (M.)	5·48 (S.)	4·67 (M.)	4·49 (M.)	3·61 (V.W.)	3·49 (F.S.)
3·34 (V.W.)	3·21 (V.S.)	3·12 (V.W.)	3·01 (W.)	2·84 (M.)	2·73 (V.W.)
2·59 (W.)	2·51 (W.)	2·45 (W.)	2·39 (W.)	2·32 (V.W.)	2·18 (V.W.)
2·09 (W.)					

This pattern was given both by an authentic specimen and by gallic acid obtained by hydrolysis of (−)-gallocatechin gallate.

Triacetylgallic acid.

9·64 (M.)	8·44 (V.S.)	7·70 (M.)	6·82 (F.S.)	6·61 (M.)	5·96 (F.S.)
5·38 (V.W.)	4·86 (F.S.)	4·25 (M.)	4·17 (M.)	3·93 (M.)	3·68 (V.S.)
3·60 (F.S.)	3·44 (W.)	3·37 (V.W.)	3·26 (W.)	3·12 (V.W.)	3·00 (W.)
2·91 (V.W.)	2·78 (V.W.)	2·68 (W.)	2·61 (W.)	2·52 (V.W.)	2·42 (V.W.)
2·31 (V.W.)	2·20 (V.W.)				

This pattern was given both by an authentic specimen and by triacetyl gallic acid obtained by hydrolysis of (−)-gallocatechin gallate.

(−)-epi*Catechin gallate.*

7·97 (V.W.)	7·03 (V.W.)	6·37 (M.)	5·87 (V.W.)	5·46 (V.W.)	5·20 (V.S.)
5·02 (V.W.)	4·82 (V.W.)	4·62 (W.)	4·38 (W.)	4·21 (W.)	4·03 (V.W.)
3·95 (V.W.)	3·80 (S.)	3·69 (V.W.)	3·47 (V.W.)	3·38 (S.)	3·25 (W.)
3·10 (M.)	2·95 (V.W.)	2·84 (M.)	2·75 (W.)	2·61 (W.)	2·49 (W.)
2·37 (M.)	2·26 (W.)	2·23 (V.W.)	2·11 (M.)	2·04 (W.)	1·99 (W.)
1·96 (V.W.)	1·92 (W.)	1·87 (W.)	1·81 (V.W.)	1·71 (D.W.)	1·62 (D.W.)
1·59 (V.W.)	1·56 (V.W.)	1·18 (V.W.)	1·14 (V.W.)		

Substance (2a).

10·8 (M.)	8·41 (D.W.)	7·32 (D.W.)	7·00 (W.)	6·62 (V.W.)	5·93 (M.)
5·41 (M.)	5·12 (V.W.)	4·69 (M.)	4·46 (V.W.)	4·21 (S.)	3·97 (V.W.)
3·80 (V.S.)	3·62 (W.)	3·37 (D.F.S.)	3·14 (W.)	2·98 (W.)	2·88 (W.)
2·74 (M.)	2·63 (D.W.)	2·57 (W.)	2·46 (V.W.)	2·38 (W.)	2·32 (V.W.)
2·27 (V.W.)	2·10 (W.)	2·05 (W.)	1·91 (W.)	1·86 (W.)	

Acetyl derivative of substance (2b).

14·8 (V.W.)	13·0 (V.S.)	11·0 (W.)	9·7 (V.W.)	8·95 (V.S.)	8·11 (V.W.)
7·52 (M.)	6·92 (W.)	6·40 (V.W.)	6·05 (V.W.)	5·49 (F.S.)	5·11 (F.S.)
4·95 (V.S.)	4·69 (M.)	4·41 (F.S.)	4·24 (F.S.)	4·11 (F.S.)	3·93 (F.S.)
3·81 (F.S.)	3·62 (V.W.)	3·52 (V.W.)	3·45 (S.)	3·37 (W.)	3·24 (V.W.)
3·11 (V.W.)	2·92 (M.)	2·76 (V.W.)	2·61 (V.W.)	2·52 (V.W.)	2·45 (V.W.)
2·28 (D.W.)	2·18 (W.)	2·08 (W.)	2·00 (D.W.)	1·86 (D.W.)	1·79 (V.W.)
1·73 (D.W.)					

(−)-epi*Catechin acetate.*

16·3 (F.S.)	13·16 (W.)	9·90 (M.)	8·66 (W.)	7·36 (W.)	6·55 (M.)
6·24 (M.)	5·70 (W.)	5·42 (M.)	5·20 (W.)	4·93 (M.)	4·76 (M.)
4·52 (W.)	4·30 (S.)	4·19 (S.)	4·00 (W.)	3·80 (W.)	3·61 (S.)
3·40 (M.)	3·27 (W.)	3·10 (V.W.)			

This pattern was given by the acetyl derivatives of (−)-*epi*catechin from *Acacia catechu*, substance (3), and an hydrolysis product of substance (2).

(−)-*Gallocatechin gallate.*

10·3 (M.)	8·58 (W.)	7·34 (M.)	6·77 (V.W.)	6·22 (V.W.)	5·96 (V.W.)
5·66 (M.)	5·43 (V.W.)	5·21 (M.)	5·01 (V.W.)	4·84 (V.W.)	4·56 (F.S.)
4·42 (V.W.)	4·29 (F.S.)	4·13 (F.S.)	3·95 (V.W.)	3·86 (V.W.)	3·76 (W.)
3·63 (V.S.)	3·44 (S.)	3·37 (V.W.)	3·19 (M.)	3·09 (F.S.)	3·01 (W.)
2·86 (W.)	2·75 (W.)	2·65 (W.)	2·53 (M.)	2·45 (V.W.)	2·43 (F.S.)
2·32 (D.W.)	2·23 (V.W.)	2·15 (M.)	2·04 (W.)	2·00 (V.W.)	1·94 (M.)
1·89 (W.)	1·85 (V.W.)	1·80 (V.W.)	1·77 (V.W.)	1·68 (D.W.)	1·61 (V.W.)
1·56 (V.W.)					

This work was carried out partly under the auspices of the Research Committee of the Indian Tea Association and partly as an investigation by the Laboratories of J. Lyons and Co. Ltd. The authors wish to thank Miss D. M. Brasher and Miss B. A. Jackman for the spectrophotometric work, and Miss W. B. Wright for the Debye–Scherrer photographs. They also wish to thank Dr. L. H. Lampitt for his continued interest.

INDIAN TEA ASSOCIATION.
LYONS LABORATORIES.

[*Received, February 28th,* 1948.]

---

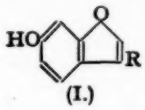
457. *Furano-compounds. Part VII. A Synthesis of 2 : 3-Dihydropsoralene.*

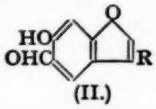
By R. T. FOSTER, ALEXANDER ROBERTSON, and (in part) ANIS BUSHRA.

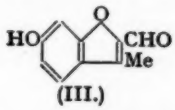
The product obtained by the application of Gattermann's aldehyde synthesis to 6-hydroxy-3-methylcoumarone has been shown to be the 2-formyl derivative. Attempts to prepare 6-hydroxy-2-carbethoxy-5-formylcoumarone required for the synthesis of psoralene were unsuccessful, but dihydropsoralene and its 3-methyl derivative have been synthesised from the requisite coumarans.

IN the course of synthetical experiments in this group of compounds, it has been established that the application of the Gattermann reaction for the synthesis of aldehydes to 3-methylcoumarones, having a free 2-position, invariably gives rise to the 2-formyl derivatives (*J.*, 1938, 306; 1939, 92, 1594; and unpublished work) and consequently it became clear that *o*-hydroxyaldehydes of the type (II) required as intermediates for the rational synthesis of furanocoumarins by the route employed in the case of *allo*bergapten (Part IV, *J.*, 1939, 930) cannot be obtained by this procedure unless the 2-position of the coumarone ring is first protected by a group which can be conveniently eliminated at a later stage in the synthesis.

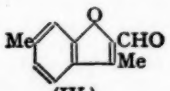
This conclusion was clearly at variance with the claims of Karrer and his co-workers (*Helv. Chim. Acta*, 1920, **3**, 541) who, in the course of attempts to synthesise furanocoumarins of the bergapten type, applied the Gattermann reaction to 6-hydroxy- and to 6-hydroxy-3-methylcoumarone, obtaining products which they considered to have structures (II; R = H) and (II; R = Me). When it was found that the aldehydes gave the corresponding acrylic acids by the Perkin reaction but not the expected coumarins, these authors suggested that the failure of the latter acids to undergo cyclisation was due to their existence as *trans*-isomerides (compare Karrer and co-workers, *Helv. Chim. Acta*, 1921, **4**, 718). Before proceeding with synthetical work on psoralene and related furanocoumarins it seemed desirable to re-examine the aldehydes obtained from (I; R = H) and (I; R = Me), more especially in view of the claim of Rây and his co-workers (*J.*, 1935, 813) that the acrylic acid obtained by the hydration of 3′-methylfurano(5′ : 4′ : 7 : 6)coumarin in ultraviolet light was identical with that synthesised by the Swiss workers from the aldehyde which they considered to have formula (II; R = Me).

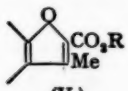

(I.)


(II.)


(III.)

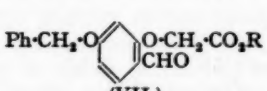
In agreement with the earlier results obtained in these laboratories (*loc. cit.*), the aldehyde from 6-hydroxy-3-methylcoumarone (I; R = Me), which appears to be identical with that described by Karrer and his co-workers (*loc. cit.*), has been shown to have the structure (III), since on oxidation its *acetate* gave rise to *6-acetoxy-3-methylcoumarone-2-carboxylic acid*, identical with the acetate of an authentic specimen of 6-hydroxy-3-methylcoumarone-2-carboxylic acid. Consequently, the acrylic acid and its methyl ether (Karrer and co-workers, *loc. cit.*) formed from the aldehyde (III) by Perkin's method is β-6-hydroxy-3-methylcoumarone-2-acrylic acid and its methyl ether. Unlike Karrer and his co-workers, we failed to obtain a crystalline product by application of the Gattermann reaction to 6-hydroxycoumarone (I; R = H) with or without zinc chloride or aluminium chloride as an auxiliary condensing agent (compare Part II, *J.*, 1939, 921). It seems probable that in our experiments the initial condensation product was the required aldimine but that the hydrolysis of the latter was accompanied by polymerisation of the resulting aldehyde (compare thiophen, Barger and Sasson, *J.*, 1938, 2600; and 4-hydroxycoumarone, Manjunath *et al.*, *Ber.*, 1939, **72**, 93).

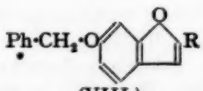

(IV.)

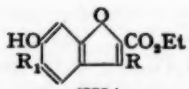

(V.)

(VI.)

A further example of the behaviour of coumarones of the type (I) when subjected to Gattermann's aldehyde synthesis is seen in the case of 3 : 6-dimethylcoumarone which gives rise to *2-formyl-3 : 6-dimethylcoumarone* (IV), the orientation of which is established by its oxidation to *3 : 6-dimethylcoumarone-2-carboxylic acid* (V; R = H), identical with a specimen prepared by cyclisation of *ethyl 2-acetyl-5-methylphenoxyacetate* (VI) and hydrolysis of the resulting *ester* (V; R = Et). *3 : 6-Dimethylcoumarone-2-acetic acid*, an analogue of pyrousnic acid, was synthesised from 2-formyl-3 : 6-dimethylcoumarone (IV) according to the general method (*J.*, 1938, 306).

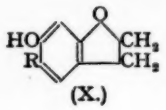

(VII.)

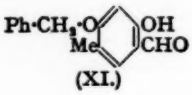

(VIII.)

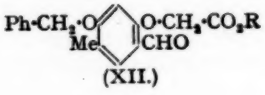

(IX.)

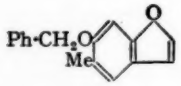
In deciding to attempt a synthesis of psoralene by the route employed for *allo*bergapten (Part IV, *loc. cit.*), *i.e.* by way of the aldehyde (IX; R = H, R_1 = CHO), we expected to be able to prepare the latter compound by application of the Gattermann reaction to *6-hydroxy-2-carbethoxycoumarone* (IX; R = R_1 = H), which was obtained by the cyclisation of the *phenoxyacetate* (VII; R = Et) with alcoholic sodium ethoxide and subsequent debenzylation of the resulting *carbethoxycoumarone* (VIII; R = CO_2Et) by hydrogenolysis. It was found, however, that (IX; R = R_1 = H) as well as its homologue (IX; R = Me, R_1 = H), prepared in a similar way from the *ester* (XV; R = Et), failed to yield formyl derivatives when subjected to Gattermann's reaction or the usual variations of it. In connection with the hydrogenolysis

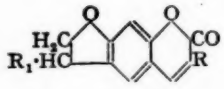
of (VIII; R = CO_2Et) with a palladium–charcoal catalyst it is noteworthy that, as in the case of 2-carbethoxy-6-benzyloxy-4-methoxycoumarone (Part IV, *loc. cit.*), the α-carbethoxy-group in (VIII; R = CO_2Et) inhibits the hydrogenation of the double bond of the furan residue. Moreover, in the present instance this inhibitory effect is sufficient to allow the hydrogenation of (VIII; R = CO_2Et) by means of Adams's platinum catalyst with the formation of *2-carbethoxy-6-hexahydrobenzyloxycoumarone*, in which the retention of the furan ring is confirmed by the fact that this product gives the same intense sulphuric acid reaction as the parent substance (VIII; R = CO_2Et). Under the conditions employed, this platinum catalyst does not effect hydrogenolysis of benzyl ethers.


(X.)

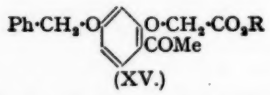

(XI.)

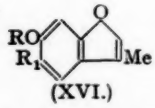

(XII.)

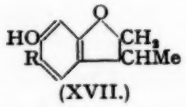
(XIII.) 


(XIV.)

Having failed to obtain the required intermediate aldehyde, we abandoned for the present the project of synthesising psoralene by the route employed for *allo*bergapten (*loc. cit.*) and turned our attention to a rational synthesis of its 2 : 3-dihydro-derivative (XIV; R = R_1 = H) which Späth and his co-workers (*Ber.*, 1936, **69**, 1087) have shown can be dehydrogenated to yield psoralene. This objective was achieved as follows. *6-Benzyloxycoumarone* (VIII; R = H) was prepared by cyclisation of *5-benzyloxy-2-formylphenoxyacetic acid* (VII; R = H) with simultaneous decarboxylation of the resulting acid (VIII; R = CO_2H) and on hydrogenation gave rise to 6-hydroxycoumaran in good yield. The *aldehyde* obtained from the latter compound is shown to have the structure (X; R = CHO) because on reduction by Clemmensen's method it yielded *6-hydroxy-5-methylcoumaran* (X; R = Me), identical with a specimen prepared from (XI) by way of the stages (XII; R = Et), (XII; R = H), and (XIII). The condensation of (X; R = CHO) with cyanoacetic acid followed by hydrolysis of the initial product gave rise to the *acid* (XIV; R = CO_2H, R_1 = H), and on decarboxylation the latter furnished dihydropsoralene (XIV; R = R_1 = H) which was dehydrogenated by being heated with palladium-black, yielding psoralene.

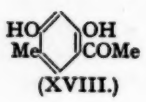

(XV.)

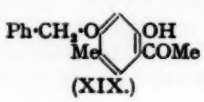

(XVI.)

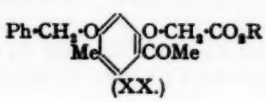

(XVII.)

Similarly *3′-methyldihydropsoralene* (XIV; R = H, R_1 = Me) was synthesised from *ethyl 5-benzyloxy-2-acetylphenoxyacetate* (XV; R = Et) by way of the stages (XV; R = H), (XVI; R = CH_2Ph, R_1 = H), (XVII; R = H), (XVII; R = CHO), and (XIV; R = CO_2H, R_1 = Me).

In connection with the latter synthesis it may be noted that Karrer and Widmer (*Helv. Chim. Acta*, 1919, **2**, 454) claim to have obtained 6-hydroxy-3-methylcoumaran (XVII; R = H), m. p. 96°, by reduction of 6-hydroxy-3-methylcoumarone (I; R = Me), m. p. 103°, with sodium and alcohol and from this reduction product to have prepared the aldehyde (XVII; R = CHO), m. p. 185°. Repeated attempts in this laboratory to reduce 6-hydroxy-3-methylcoumarone according to the directions of the Swiss workers gave only slightly impure starting material, m. p. 98—100°. On the other hand, hydrogenation of *6-benzyloxy-3-methylcoumarone* (XVI; R = CH_2Ph, R_1 = H) gave rise to *6-hydroxy-3-methylcoumaran* (XVII; R = H), m. p. 62°, which furnished the *aldehyde* (XVII; R = CHO), m. p. 74°. The orientation of the latter compound is established by the fact that on reduction it yields *6-hydroxy-3 : 5-dimethylcoumaran* (XVII; R = Me), identical with a specimen obtained by simultaneous hydrogenation and debenzylation of *6-benzyloxy-3 : 5-dimethylcoumarone* (XVI; R = CH_2Ph, R_1 = Me). In our opinion the aldehyde, m. p. 185°, obtained in small yield by Karrer and his co-workers is clearly the 2-formylcoumarone (III), formed from unchanged (I; R = Me).


(XVIII.)


(XIX.)


(XX.)

In the synthesis of (XVI; R = CH_2Ph, R_1 = Me) the ketone (XVIII) was converted into the *monobenzyl ether* (XIX), and on condensation with ethyl bromoacetate by the potassium carbonate–acetone method this ether (XIX) gave rise to the *phenoxy*-ester (XX; R = Et), which on hydrolysis furnished the *acid* (XX; R = H). Cyclisation of the latter compound by the standard procedure yielded the coumarone (XVI; R = CH_2Ph, R_1 = Me). The orientation of (XX; R = Et) and consequently of (XIX) follows from the successful conversion of the acid (XX; R = H) into a coumarone.

Experimental.

2-Carbethoxy-6-benzyloxycoumarone (VIII; R = CO_2Et).—Interaction of 2-hydroxy-4-benzyloxybenzaldehyde (10 g.), ethyl bromoacetate (8·5 g.), and potassium carbonate (15 g.) in boiling acetone (100 ml.) during 3 hours gave *ethyl 5-benzyloxy-2-formylphenoxyacetate* (VII; R = Et) which formed needles (12 g.), m. p. 88°, from light petroleum (b. p. 60—80°) (Found: C, 68·7; H, 5·8. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%). On addition of alcoholic sodium ethoxide (from 0·75 g. of sodium and 50 ml. of alcohol) a solution of the foregoing ester (10 g.) in alcohol (175 ml.) became yellow and in the course of 5 minutes deposited a yellow amorphous solid which dissolved on dilution with water and was replaced by a crystalline precipitate of *ethyl 6-benzyloxycoumarone-2-carboxylate* (VIII; R = CO_2Et). Recrystallised from aqueous alcohol, this compound formed colourless plates (6·5 g.), m. p. 94°, having a violet, becoming blue-violet, sulphuric acid reaction (Found: C, 73·0; H, 5·5. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%). The yield of this product was not improved by the use of potassium ethoxide. Acidification of the aqueous alcoholic liquors with hydrochloric acid furnished *5-benzyloxy-2-formylphenoxyacetic acid* (VII; R = H) which separated from water in needles, m. p. 145° (Found: C, 67·2; H, 4·8. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%).

Debenzylation of the ester (VIII; R = CO_2Et) (2 g.), dissolved in acetic acid (50 ml.), was effected with hydrogen and a palladium–charcoal catalyst (from 0·2 g. of palladium chloride and 2 g. of charcoal) in 15 minutes, and on isolation *6-hydroxy-2-carbethoxycoumarone* (IX; R = R_1 = H) formed colourless plates (1·2 g.), m. p. 156°, from aqueous alcohol (Found: C, 64·5; H, 5·0. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). A solution of the compound in warm sulphuric acid became blue-violet and then purple. Formed by the pyridine method, the *acetate* was obtained in rectangular plates, m. p. 104°, from alcohol (Found: C, 62·7; H, 4·9. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%).

When 6-benzyloxy-2-carbethoxycoumarone (1 g.) was hydrogenated with a platinum oxide catalyst (0·1 g.) in acetic acid (30 ml.) during 2½ hours, a compound was obtained which appeared to be *2-carbethoxy-6-hexahydrobenzyloxycoumarone*, forming plates (0·5 g.), m. p. 91°, from alcohol (Found: C, 71·4; H, 7·3. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·3%). That the furano-system had not been hydrogenated was shown by the fact that the compound gave the same intense blue-violet sulphuric acid reaction as the parent substance.

Hydrolysis of 6-hydroxy-2-carbethoxycoumarone (5 g.) with 2N-aqueous sodium hydroxide (100 ml.) on the steam-bath for ½ hour gave 6-hydroxy-2-carboxycoumarone, m. p. 257—259°, after purification from water (compare Karrer *et al.*, *loc. cit.*), which yielded the *acetate*, forming rectangular prisms, m. p. 213°, from aqueous acetone (Found: C, 60·0; H, 3·8. $C_{11}H_8O_5$ requires C, 60·0; H, 3·6%). Decarboxylation of this acid (2 g.) in boiling quinoline (10 ml.) containing copper-bronze (2 g.) was complete in 10 minutes, and on isolation the resulting 6-hydroxycoumarone was purified by distillation in a high vacuum and then by crystallisation from light petroleum (b. p. 40—60°), forming long needles m. p. 56° (compare Karrer *et al.*, *loc. cit.*).

6-Hydroxy-5-formylcoumaran (X; R = CHO).—On being refluxed with acetic anhydride (100 ml.) and sodium acetate (25 g.) 5-benzyloxy-2-formylphenoxyacetic acid (VII; R = H) (10 g.) gave an oil which on distillation in a high vacuum furnished *6-benzyloxycoumarone* (VIII; R = H) (6 g.), b. p. 140—142°/0·3 mm., m. p. 39°, having a cherry-red sulphuric acid reaction (Found: C, 80·3; H, 5·4. $C_{15}H_{12}O_2$ requires C, 80·4; H, 5·4%). Hydrogenation and simultaneous debenzylation of this ether (3 g.), dissolved in acetic acid (50 ml.), with hydrogen and a palladium–charcoal catalyst gave 6-hydroxycoumaran (X; R = H) (1·5 g.), m. p. 60°, which furnished a *p-nitrobenzoate*, forming rectangular plates, m. p. 179°, from alcohol (Found: C, 62·8; H, 3·9; N, 5·1. $C_{15}H_{11}O_5N$ requires C, 63·2; H, 3·9; N, 4·9%) (compare Späth and co-workers, *Ber.*, 1936, **69**, 1087, who give the m. p. of 6-hydroxycoumaran as 61°).

Condensation of 6-hydroxycoumaran (2 g.) and hydrogen cyanide (2 ml.) was effected in ether (75 ml.) with zinc chloride (2 g.) and excess of hydrogen chloride. Next day the purple aldimine was isolated and hydrolysed with water (100 ml.) on the steam-bath for 20 minutes, giving the *5-aldehyde*, which formed colourless rectangular plates (2 g.), m. p. 113°, from aqueous alcohol and had a red-brown ferric reaction in alcohol (Found: C, 65·8; H, 5·1. $C_9H_8O_2$ requires C, 65·7; H, 4·9%). The *2 : 4-dinitrophenylhydrazone* separated from ethyl acetate in red needles, m. p. 274° (Found: N, 16·2. $C_{15}H_{12}O_5N_4$ requires N, 16·3%).

2′ : 3′-Dihydrofurano(4′ : 5′ : 6 : 7)coumarin (*Dihydropsoralene*) (XIV; R = R_1 = H). (With J. B. D. MacKenzie).—A solution of the foregoing aldehyde (X; R = CHO) (1 g.) in 20% aqueous sodium hydroxide (10 ml.) was treated with aqueous cyanoacetic acid (7 ml. of Phelps and Tillotson's solution, *Amer. J. Sci.*, 1908, **26**, 267). Next day the sodium salt of the salicylidenecyanoacetic acid was dissolved by addition of water (10 ml.) to the mixture, and the yellow product was precipitated with concentrated hydrochloric acid and boiled with N-hydrochloric acid (100 ml.) for ½ hour. On isolation the resulting *coumarin-3-carboxylic acid* (XIV; R = CO_2H, R_1 = H) formed almost colourless rectangular prisms (1·2 g.), m. p. 244° (decomp.), from ethyl acetate (Found: C, 62·2; H, 3·6. $C_{12}H_8O_5$ requires C, 62·1; H, 3·5%). A mixture of this acid (0·8 g.), copper-bronze (1 g.), and quinoline (4 ml.) was gently boiled (oil-bath) for 10 minutes, cooled, and diluted with ether, and the product was filtered off and washed with dilute hydrochloric acid, followed by aqueous sodium hydroxide and then water.

Evaporation of the dried ethereal solution left dihydropsoralene which, after sublimation in a high vacuum at 140—150°/0·1 mm., formed rectangular prisms, m. p. 200°, from alcohol (Found : C, 70·4; H, 4·4. Calc. for $C_{11}H_8O_3$: C, 70·2; H, 4·3%) (Späth *et al.*, *loc. cit.*, give m. p. 204°). An intimate mixture of dihydropsoralene (0·3 g.) and Willstätter palladium-black (0·3 g.) was kept at 170—180° for 11 hours. On isolation, the resulting psoralene was purified by sublimation in a vacuum and then by crystallisation from water, forming needles, m. p. 167° (compare Späth *et al.*, *loc. cit.*).

Application of the Perkin reaction to 6-hydroxy-5-formylcoumaran gave rise to a mixture containing *β-6-acetoxycoumarone-5-acrylic acid*, forming prismatic needles, m. p. 197°, from aqueous acetone (Found : C, 63·0; H, 4·8. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%), along with unchanged aldehyde and its acetate. The latter derivative was characterised by formation of the 2 : 4-*dinitrophenylhydrazone*, which separated from acetic acid in orange-red prisms, m. p. 266° (Found : C, 53·0; H, 3·8; N, 14·7. $C_{17}H_{14}O_7N_4$ requires C, 53·1; H, 3·9; N, 14·5%).

5-Benzyloxy-2-formyl-4-methylphenoxyacetic Acid (XII; R = H).—The condensation of 4-methylresorcinol (9 g.) and hydrogen cyanide (8 ml.) in ether (200 ml.) was effected with hydrogen chloride, and the resulting aldimine hydrolysed with water (200 ml.) on the steam-bath for ½ hour, giving 5-methylresorcylaldehyde, which formed plates (7 g.), m. p. 146°, from benzene (compare Gattermann, *Annalen*, 1907, **357**, 340). A mixture of this aldehyde (3 g.), benzyl bromide (3·7 g.), potassium carbonate (5 g.), and acetone (50 ml.) was refluxed for 4 hours. On isolation, the solid product was dissolved in ether (250 ml.), the solution was extracted with dilute aqueous sodium hydroxide (200 ml. × 2), the combined extracts were acidified with dilute hydrochloric acid, and the precipitate collected, washed, and crystallised from dilute alcohol, giving 4-O-*benzyl-5-methylresorcylaldehyde* (XI) in colourless needles (1·5 g.), m. p. 65° (Found : C, 74·0; H, 6·0. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%). This compound gives a dark reddish-purple ferric reaction in alcohol.

Interaction of this aldehyde (2 g.), ethyl bromoacetate (1·5 g.), and potassium carbonate (3 g.) in boiling acetone (50 ml.) during 7 hours gave rise to *ethyl 5-benzyloxy-2-formyl-4-methylphenoxyacetate* (XII; R = Et) which formed colourless prisms (2 g.), m. p. 93°, from dilute alcohol, having a negative ferric reaction (Found : C, 69·6; H, 6·0. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%). A solution of this ester (2 g.) in alcohol (30 ml.) and water (20 ml.) containing potassium hydroxide (2·5 g.) was refluxed for ½ hour, the greater part of the alcohol was removed in a vacuum, and the residual liquor was cooled and acidified with dilute hydrochloric acid. Crystallisation of the resulting precipitate from ethyl acetate–light petroleum (b. p. 60—80°) gave the *acid* (XII; R = H) in colourless needles (1·5 g.), m. p. 185° (Found : C, 67·9; H, 5·2. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%).

6-Hydroxy-5-methylcoumaran (X; R = Me).—(A) A mixture of the foregoing acid (2 g.), sodium acetate (5 g.), and acetic anhydride (20 ml.) was refluxed (oil-bath) for ½ hour, and the mixture diluted with water (200 ml.). Three days later the product was collected, washed with aqueous sodium hydrogen carbonate, dried, and distilled in a high vacuum, giving *6-benzyloxy-5-methylcoumarone* (XIII), b. p. 110°/0·03 mm., which formed colourless needles (1·0 g.), m. p. 38°, from 50% acetic acid, having a port-wine sulphuric acid reaction (purple in warm acid) (Found : C, 80·4; H, 6·0. $C_{16}H_{14}O_2$ requires C, 80·7; H, 5·8%). Hydrogenation of this compound (1 g.), dissolved in acetic acid (150 ml.), with hydrogen and a palladium–charcoal catalyst (from 1 g. of charcoal and 0·1 g. of palladium chloride) gave rise to *6-hydroxy-5-methylcoumaran*, which was isolated by evaporation of the filtered reaction mixture, washed with aqueous sodium hydrogen carbonate, and crystallised from carbon tetrachloride, forming colourless, irregular plates (0·5 g.), m. p. 154° (Found : C, 71·9; H, 6·8. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%). This substance is soluble in alcohol, ethyl acetate, or benzene and has a negative ferric reaction and a negative sulphuric acid reaction. The *p-nitrobenzoate* of this coumaran formed pale yellow, hexagonal plates, m. p. 176°, from alcohol (Found : N, 4·7. $C_{16}H_{13}O_5N$ requires N, 4·7%).

(B) A mixture of 6-hydroxy-5-formylcoumaran (2 g.), zinc amalgam (from 16 g. of zinc), concentrated hydrochloric acid (16 ml.), and water (15 ml.) was refluxed for 8 hours, and the product isolated by means of ether. Crystallised from carbon tetrachloride, the resulting 6-hydroxy-5-methylcoumaran formed colourless plates (1·3 g.), m. p. 154°, identical in every way with a specimen prepared by method (A) (Found : C, 71·7; H, 6·6%).

6-Hydroxy-2-formyl-3-methylcoumarone (III).—This aldehyde, m. p. 182—183° (slight decomp.), which was prepared according to the directions of Karrer and Widmer (*loc. cit.*) who give m. p. 181°, did not give a ferric reaction and on acetylation by the pyridine method furnished the *acetate*, forming needles, m. p. 117°, from alcohol, which on being kept in contact with the solvent changed into diamond-shaped plates, m. p. 117° (Found : C, 66·1; H, 4·5. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·5%). The 2 : 4-*dinitrophenylhydrazone* of the latter derivative separated from ethyl acetate in red needles, m. p. 275° (Found : N, 14·2. $C_{18}H_{14}O_7N_4$ requires N, 14·1%). The oxime of (III), which separated from water in long needles, had m. p. 186°, as given by Karrer and Widmer (*loc. cit.*).

Potassium permanganate (0·3 g.), dissolved in water (12 ml.), was gradually added to a solution of the acetate of the aldehyde (0·5 g.) in acetone (15 ml.), and ½ hour later the mixture was cleared with sulphur dioxide and *6-acetoxy-3-methylcoumarone-2-carboxylic acid* mixed with unchanged aldehyde was precipitated with water. Purified with the aid of aqueous sodium hydrogen carbonate, the acid formed rectangular prisms, m. p. 226°, from ethyl acetate, identical in every way with a specimen obtained by acetylation of authentic 6-hydroxy-3-methylcoumarone-2-carboxylic acid (Found : C, 61·4; H, 4·6. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%).

6-Hydroxy-3-methylcoumaran (XVII; R = H).—A mixture of 2-hydroxy-4-benzyloxyacetophenone (*J.*, 1937, 1530) (10 g.), ethyl bromoacetate (5·5 ml.), potassium carbonate (15 g.), and acetone (100 ml.) was refluxed until a sample of the product did not give a ferric reaction (about 5 hours). The resulting *ethyl 5-benzyloxy-2-acetylphenoxyacetate* (XV; R = Et) was obtained on evaporation of the filtered solution and trituration of the residue with water, and crystallised from alcohol, forming rectangular prisms (12 g.), m. p. 124° (Found : C, 69·5; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%). On hydrolysis with warm 4% aqueous-alcoholic sodium hydroxide (250 ml.) for 10 minutes this ester (10 g.) gave the *phenoxyacetic acid* (XV; R = H), forming rectangular plates (8·5 g.), m. p. 143°, from dilute acetic acid (Found : C, 68·1; H, 5·5. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%). Simultaneous cyclisation

and decarboxylation of this acid (10 g.) was effected with boiling acetic anhydride (100 ml.) and sodium acetate (25 g.) during ½ hour, and on isolation the resulting 6-*benzyloxy*-3-*methylcoumarone* (XVI; R = CH_2Ph, R_1 = H) separated from 80% acetic acid in rectangular prisms (7 g.), m. p. 80°, having a red sulphuric acid reaction (Found: C, 80·6; H, 5·9. $C_{16}H_{14}O_3$ requires C, 80·7; H, 5·9%).

Hydrogenation of the foregoing benzyl ether (3 g.) in acetic acid (50 ml.) with a palladium–charcoal catalyst was complete in 20 minutes, and after filtration the greater part of the solvent was removed in a vacuum. After the addition of water to the residue, followed by excess of sodium carbonate, 6-*hydroxy*-3-*methylcoumaran* was isolated with ether and purified by distillation in a vacuum and then by crystallisation from light petroleum (b. p. 40—60°); it formed needles (1·7 g.), m. p. 62°, having a negative sulphuric acid reaction (Found: C, 72·3; H, 6·9. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%).

3′-*Methyl*-2′ : 3′-*dihydrofurano*(4′ : 5′ : 6 : 7)*coumarin* (XIV; R = H, R_1 = Me).—Condensation of 6-hydroxy-3-methylcoumaran (XVII; R = H) (3 g.) with hydrogen cyanide (4 ml.) in ether (100 ml.) by means of zinc chloride (4 g.) and excess of hydrogen chloride gave rise to an oily product which, on being washed several times with ether and then hydrolysed with water (100 ml.) on the steam-bath for 20 minutes, yielded the 5-*formyl* derivative (XVII; R = CHO), forming colourless rectangular prisms (3 g.), m. p. 72°, from alcohol, which gave a deep red ferric reaction in alcohol (Found: C, 67·3; H, 5·7. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in scarlet needles, m. p. 282° (Found: C, 53·7; H, 4·0; N, 15·8. $C_{16}H_{14}O_6N_4$ requires C, 53·6; H, 3·9; N, 15·6%).

A solution of this aldehyde (1 g.) in 20% aqueous sodium hydroxide (10 ml.) was brought into reaction with aqueous cyanoacetic acid (7 ml.), and the yellow product precipitated by hydrochloric acid and boiled with N-hydrochloric acid (100 ml.) for ½ hour as in the case of the lower homologue (X; R = CHO). On isolation the resulting *furanocoumarin*-3-*carboxylic acid* (XIV; R = CO_2H, R_1 = Me) (1·1 g.) separated from aqueous acetone in almost colourless rectangular plates, m. p. 216° (Found: C, 63·5; H, 4·1. $C_{13}H_{10}O_5$ requires C, 63·4; H, 4·1%). Like the homologue (XIV; R = CO_2H, R_1 = H), this acid was decarboxylated by the quinoline method and gave the *dihydrofuranocoumarin* (XIV; R = H, R_1 = Me), which was purified by sublimation in a vacuum at 140—150°/0·1 mm., and then by crystallisation from methyl alcohol, forming pale yellow needles (0·4 g.), m. p. 137° (Found: C, 71·3; H, 5·1. $C_{12}H_{10}O_3$ requires C, 71·3; H, 5·0%).

6-Hydroxy-5-formyl-3-methylcoumaran (1 g.) was heated (oil-bath at 180°) with acetic anhydride and sodium acetate (1 g.) for 8 hours, and after decomposition of the excess anhydride with water an oily product was isolated by means of ether. Extraction of the ethereal solution with aqueous sodium hydrogen carbonate gave β-6-*acetoxy*-3-*methylcoumaran*-5-*acrylic acid*, which separated from aqueous acetone in needles (0·07 g.), m. p. 207° (Found: C, 64·4; H, 4·8. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·3%). From the ethereal solution left on separation of the acrylic acid, unchanged aldehyde (XVI; R = CHO) was then extracted with 4% aqueous sodium hydroxide, and finally evaporation of the residual ethereal liquors left the acetate of the aldehyde as an oil which was converted into the 2 : 4-*dinitrophenylhydrazone*, forming orange needles, m. p. 245°, from acetic acid (Found: C, 53·6; H, 4·0; N, 14·0. $C_{16}H_{14}O_7N_4$ requires C, 54·0; H, 4·0; N, 14·0%).

5-*Benzyloxy*-2-*acetyl*-4-*methylphenoxyacetic Acid* (XX; R = H).—A mixture of 5-*C*-methylresacetophenone (Yanagita, *Ber.*, 1938, **71**, 2270) (5 g.), benzyl chloride (15 g.), potassium carbonate (10 g.), and acetone (50 ml.) was refluxed for 8 hours and, after removal of the potassium salts (washed with acetone) by filtration, the solvent was evaporated and the excess of benzyl chloride removed by means of a current of steam, leaving the *benzyl ether* (XIX) as a solid which separated from alcohol in colourless needles (5 g.), m. p. 94° (Found: C, 74·9; H, 6·3. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%). This compound gave a dark red ferric reaction in alcohol.

Interaction of the foregoing benzyl ether (1 g.) and ethyl bromoacetate (0·75 g.) in boiling acetone (25 ml.), containing potassium carbonate (2 g.), for 20 hours gave rise to *ethyl* 5-*benzyloxy*-2-*acetyl*-4-*methylphenoxyacetate* (XX; R = Et), which formed colourless prisms (1 g.), m. p. 109°, from alcohol, having a negative ferric reaction (Found: C, 70·4; H, 6·6. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·4%). This ester (2 g.) was hydrolysed by being boiled with a solution of potassium hydroxide (2·5 g.) in water (20 ml.) and alcohol (30 ml.) for ½ hour. After the removal of the greater part of the alcohol in a vacuum, the residual cooled liquor was acidified with dilute hydrochloric acid and the resulting *acid* collected, washed with water, and crystallised from ethyl acetate–light petroleum (b. p. 60—80°), forming colourless prisms (1·5 g.), m. p. 156°, soluble in alcohol or hot benzene (Found: C, 68·6; H, 5·6. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%).

6-*Hydroxy*-3 : 5-*dimethylcoumaran* (XVII; R = Me).—(A) A mixture of the foregoing acid (1 g.), sodium acetate (2·5 g.), and acetic anhydride (10 ml.) was refluxed (oil-bath) for ½ hour, cooled, and diluted with water (100 ml.). Three days later the resulting 6-*benzyloxy*-3 : 5-*dimethylcoumarone* (XVI; R = CH_2Ph, R_1 = Me) was collected, washed with aqueous sodium hydrogen carbonate, and purified by distillation in a vacuum and then by recrystallisation from 50% acetic acid, being obtained in colourless needles (0·5 g.), b. p. 170°/0·02 mm., m. p. 50°, which gave a dark red sulphuric acid reaction (warm) (Found: C, 80·7; H, 6·5. $C_{17}H_{16}O_3$ requires C, 81·0; H, 6·3%). Hydrogenation of this substance (2 g.), dissolved in acetic acid (150 ml.), with hydrogen and a palladium–charcoal catalyst gave rise to 6-*hydroxy*-3 : 5-*dimethylcoumaran*, which, on isolation by the method used for the homologue (X; R = Me), formed colourless prisms (1 g.), m. p. 100°, from light petroleum (b. p. 60—80°), having a negative sulphuric acid reaction (Found: C, 73·1; H, 7·4. $C_{10}H_{12}O_3$ requires C, 73·2; H, 7·3%).

(B) A mixture of 6-hydroxy-5-formyl-3-methylcoumaran (2 g.), zinc amalgam (from 16 g. of zinc dust), water (30 ml.), and concentrated hydrochloric acid (12 ml.) was refluxed for 12 hours. On isolation with ether the resulting 6-hydroxy-3 : 5-dimethylcoumaran separated from light petroleum (b. p. 60—80°) in colourless prisms (1·2 g.), m. p. 100°, identical in every way with a specimen prepared by method (A) (Found: C, 73·5; H, 7·5%). Prepared by the pyridine method at room temperature, the p-*nitrobenzoate* of 6-hydroxy-3 : 5-dimethylcoumaran formed pale yellow, slender prisms, m. p. 145°, from alcohol (Found: N, 4·4. $C_{17}H_{17}O_5N$ requires N, 4·4%).

(With T. V. HEALEY.)

3 : 6-*Dimethylcoumarone.*—Prepared by the interaction of 2-hydroxy-4-methylacetophenone (Rosenmund and Schnurr, *Annalen*, 1927, **460**, 88) (7 g.), ethyl bromoacetate (6·2 ml.), and potassium carbonate (14 g.) in boiling acetone (40 ml.) during 12 hours, *ethyl 2-acetyl-5-methylphenoxyacetate* (VI) formed rectangular prisms (10·5 g.), m. p. 76°, from light petroleum (b. p. 60—80°) (Found: C, 66·3; H, 6·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%). Hydrolysis of this ester (6 g.) with 5% aqueous-alcoholic potassium hydroxide (120 ml.) on the steam-bath for one hour gave *2-acetyl-5-methylphenoxyacetic acid* (4 g.), which separated from water in plates, m. p. 142° (Found: C, 63·5; H, 5·7.. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%). On being boiled with acetic anhydride (60 ml.) and sodium acetate (25 g.) for 40 minutes, this acid (10 g.) yielded the coumarone which, on isolation with ether and distillation in a vacuum, was obtained as a colourless oil, b. p. 109—112°/22 mm., formed a picrate, m. p. 76°, and gave a violet-red colour with sulphuric acid changing to blue on addition of a little water (compare Stoermer, *Annalen*, 1900, **312**, 290).

Cyclisation of ethyl 2-acetyl-5-methylphenoxyacetate (5 g.), dissolved in the minimum amount of alcohol, with sodium ethoxide (from 0·25 g. of sodium) on the steam-bath during one hour and subsequent addition of water (150 ml.) to the cooled reaction mixture gave ethyl 3 : 6-dimethylcoumarone-2-carboxylate, which formed slender needles (1·6 g.), m. p. 42°, from dilute methyl alcohol. Acidification of the alkaline liquor left on separation of the ester gave 3 : 6-*dimethylcoumarone-2-carboxylic acid* (V; R = H) (1·8 g.), which separated from benzene in tiny rectangular prisms, m. p. 220° (decomp.) (Found: C, 69·5; H, 5·2. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). The acid, which was also obtained by hydrolysis of the ester with 7% aqueous-alcoholic potassium hydroxide on the steam-bath for ½ hour, gave an intense scarlet-red coloration with alcoholic ferric chloride and a red sulphuric acid reaction (warm).

2-*Formyl*-3 : 6-*dimethylcoumarone* (IV).—3 : 6-Dimethylcoumarone (2 g.) was added to a solution of aluminium chloride (4 g., 2 mols.) in ether (70 ml.) followed by hydrogen cyanide (0·5 ml.), and the mixture saturated with hydrogen chloride. Next day the almost colourless crystalline product was separated from the dark green liquor, thoroughly washed with ether, and treated with ice and dilute hydrochloric acid, and the mixture was warmed on the water-bath for ½ hour, giving rise to the *aldehyde*, which formed prismatic needles, m. p. 81°, from alcohol (Found: C, 75·9; H, 5·9. $C_{11}H_{10}O_2$ requires C, 75·9; H, 5·7%). A further quantity of the compound (0·6 g.) was obtained by extracting the combined ethereal liquors with water and warming the extract on the water-bath. The 2 : 4-*dinitrophenylhydrazone* separated from much ethyl acetate in tiny, dark red, rectangular prisms, m. p. 278° (Found: N, 16·0. $C_{17}H_{14}O_5N_4$ requires N, 15·8%).

When the foregoing reaction was carried out with 1 mol. of aluminium chloride, with excess of zinc chloride, and without an auxiliary condensing agent the respective yields of aldehyde from 2 g. of coumarone were 1·2 g., 0·9 g., and 0·2 g. The orientation of this aldehyde was established by the fact that on oxidation in acetone with aqueous potassium permanganate it gave rise to 3 : 6-dimethylcoumarone-2-carboxylic acid, m. p. 220° (decomp.), after purification from benzene, identical with an authentic specimen.

3 : 6-*Dimethylcoumarone-2-acetic Acid.*—Condensation of the aforementioned aldehyde (6 g.) with hippuric acid (10 g.) by means of acetic anhydride (40 ml.) and sodium acetate (6 g.) on the steam-bath for 1½ hours yielded the *azlactone*, which separated from alcohol in long orange needles (9 g.), m. p. 168° (Found: C, 75·8; H, 4·7; N, 4·4. $C_{20}H_{15}O_3N$ requires C, 75·7; H, 4·7; N, 4·4%). Hydrolysis of this compound (10 g.) with boiling 10% aqueous sodium hydroxide (160 ml.) for 6 hours gave 3 : 6-dimethylcoumarone-2-pyruvic acid which, on being separated from the accompanying benzoic acid by the sulphur dioxide method, formed pale yellow plates (2·5 g.), m. p. 208° (decomp.), from alcohol. Oxidation of the pyruvic acid (1 g.), dissolved in 5% aqueous sodium hydroxide (20 ml.), with 30% hydrogen peroxide (1·6 ml.) in the course of one hour furnished an almost theoretical yield of 3 : 6-*dimethylcoumarone-2-acetic acid*, which separated from dilute alcohol in colourless rectangular plates, m. p. 153°, having a cherry-red sulphuric acid reaction (Found: C, 70·4; H, 6·0. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%).

The authors are indebted to Messrs. Imperial Chemical Industries Limited for a grant in aid of this investigation.

UNIVERSITY OF LIVERPOOL. [*Received, January 22nd*, 1948.]

---

458. *Furano-compounds. Part VIII. The Synthesis of* iso*Visnagin and a Partial Synthesis of Visnagin.*

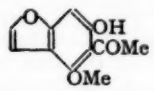
By J. R. CLARKE, GEORGE GLASER, and ALEXANDER ROBERTSON.

The partial synthesis of visnagin from natural visnagone (I) and its condensation with piperonal to form a styryl derivative afford decisive evidence that visnagin is a furanochromone type (III). In the course of unsuccessful attempts to prepare visnagone the isomeric ketone, 6-hydroxy-4-methoxy-7-acetylcoumarone, has been obtained from which the furanochromone *iso*visnagin (VI; R = Me) has been synthesised. The transformation of visnagin into *iso*visnagin is described.

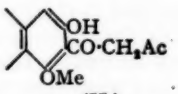
FROM a study of the hydrolytic fission of visnagin, occurring in the seeds of *Ammi visnaga*, and the subsequent degradation of the ketone visnagone thus formed, Späth and his collaborators (*Ber.*, 1941, **74**, 1492) concluded that the parent compound was the linear furanochromone (III) but the evidence presented, though it clearly shows that in visnagone (I) the acetyl residue

is in the 5-position, does not exclude the possibility of visnagin being the linear isomeric 4-methylfuranocoumarin. Accordingly, the experiments now described had as their objective a rational synthesis of visnagin.

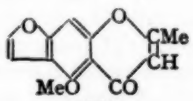
In considering a general synthetical approach to compounds of the type (III) it appeared to us more feasible in the first instance to attempt to build up the γ-pyrone system on a suitable coumarone residue rather than to form the furanochromone from an already existing hydroxychromone, more especially since this kind of procedure had already been successfully employed in the synthesis of furanocoumarins (Part IV, *J.*, 1939, 930, and unpublished work). Further, the final two stages of this process had already been used in the formation of furanochromones prepared to demonstrate the orientation of *O*-monomethylusnetol (Curd and Robertson, *J.*, 1933, 1173; the first synthesis of a furanochromone) and of euparin and tetrahydroeuparin (Kamthong and Robertson, *J.*, 1939, 933). As a preliminary step in the present investigation therefore, it has been shown that 5-methoxy-2-methylfurano(4′ : 5′ : 6 : 7)chromone (III), identical in every way with visnagin, can be conveniently synthesised by the cyclisation of the *diketone* (II) resulting from the interaction of visnagone (I) from natural sources with ethyl acetate in the presence of sodium. Further, the condensation of (III), natural or synthetical, with piperonal to give a *2-styrylchromone* is in agreement with the 2-methylchromone structure assigned to visnagin.



(I.)

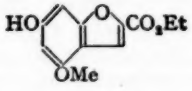


(II.)

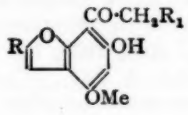


(III.)

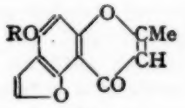
The stages required to complete the synthesis of visnagin, *viz.*, the preparation of visnagone (I), have not yet been achieved, and the remaining experiments described were occasioned primarily on this account but led ultimately to a successful synthesis of one of the two possible angular isomerides of visnagin which we have termed iso*visnagin* (VI; R = Me) and which we suspect may be a minor constituent of the seeds.



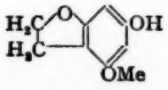
(IV.)



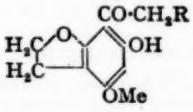
(V.)



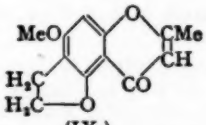
(VI.)



(VII.)



(VIII.)

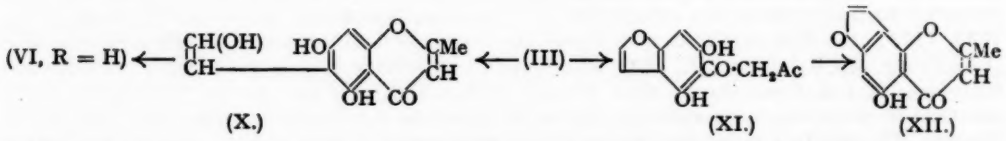


(IX.)

Application of the Hoesch reaction with acetonitrile, or of the Friedel–Crafts reaction with acetyl chloride, to the coumarone (IV), where the carbethoxy-group serves to protect the reactive 2-position (compare Part II, *J.*, 1939, 921; Part IV, *loc. cit.*), gave only one *C*-acetyl derivative of (IV). This compound must have the structure (V; R = CO_2Et, R_1 = H), because on hydrolysis and subsequent decarboxylation of the resulting *keto-acid* (V; R = CO_2H, R_1 = H) it gave rise to a *ketone* isomeric and not identical with visnagone. Since visnagone has been shown to have the *C*-acetyl group in the 5-position the synthetical ketone, which we have named *iso*visnagone and which gives a ferric reaction in alcohol indicating the presence of a hydroxyl group in the *o*-position to a carbonyl group, must be the *7-acetyl* derivative (V; R = R_1 = H). It is noteworthy that the behaviour of (IV) with the Hoesch and the Friedel–Crafts reaction is analogous to that with the Gattermann reaction (Part IV, *loc. cit.*). From the ketone (V, R = R_1 = H), *iso*visnagin (VI; R = Me) was synthesised by way of the *diketone* (V; R = H, R_1 = Ac) according to the procedure employed for visnagin. Similarly, the application of the Friedel–Crafts reaction to 6-hydroxy-4-methoxycoumaran (VII) gave only the *7-acetylcoumaran* (VIII; R = H), identical with a specimen prepared by the hydrogenation of *iso*visnagone (V, R = R_1 = H), and on condensation with ethyl acetate this ketone (VIII; R = H) gave rise to the *diketone* (VIII; R = Ac) the cyclisation of which furnished *dihydroisovisnagin* (IX).

In a projected synthesis of *O*-methylvisnagone, 2 : 6-*dimethoxy*-4-*allyloxyacetophenone* was transformed into 4-*hydroxy*-2 : 6-*dimethoxy*-3-*allylacetophenone* but so far we have been unable to determine the conditions whereby the *acetate* of the latter could be degraded to the required *o*-acetoxyphenylacetaldehyde which on deacetylation and subsequent cyclisation would be expected to give *O*-methylvisnagone, a specimen of which is readily formed by methylation of visnagone by the methyl iodide–potassium carbonate method.

The syntheses of *methyl* 2 : 6-*dihydroxy*-4-*methoxy*-3-*formyl*- and -3-*acetyl*-*benzoate* were effected in view of their possible conversion into visnagone.



In an attempt to prepare the parent hydroxyfuranochromone from visnagin (III) by demethylation it was found that the latter on being gently refluxed with concentrated hydriodic acid gave rise to a somewhat resinous product from which a well-crystallised phenolic compound was isolated. This substance, which was soluble in alkali and had only a very faint ferric reaction, gave *iso*visnagin on methylation and is therefore the *furanochromone* (VI; R = H). The identity of *iso*visnagin obtained by this route with authentic material was confirmed by the preparation of the characteristic *styryl* derivative from piperonal, and by the fact that on hydrolytic fission with boiling 20% aqueous potassium hydroxide it gave rise to *iso*visnagone identical with a synthetical specimen. The formation of nor*iso*visnagin (VI; R = H) in this manner was entirely unexpected because, although isomerides of norvisnagin could arise during the demethylation process by either of the following routes, *viz.* (*a*) opening of the furan ring with the formation of (X) followed by re-cyclisation involving the 5-hydroxyl group to give the angular compound nor*iso*visnagin (VI; R = H) or (*b*) opening of the γ-pyrone ring to yield the intermediate diketone (XI) and subsequent cyclisation to form the alternative angular product (XII), yet only the latter change (*b*) was envisaged by analogy with the behaviour of wogonin and its ethers on demethylation (Wesseley and co-workers, *Monatsh.*, 1930, **56**, 97; 1932, **60**, 26; Hattori, *Ber.*, 1939, **72**, 1914; Saski and Seshadri, *Proc. Indian Acad. Science*, 1946, **24**, No. 2, Section A, 243). Clearly, however, the process (*a*) prevails, and in spite of a careful search a second crystalline product of the hydriodic acid reaction could not be isolated from the residues left on the purification of (VI; R = H). Thus at present we have no evidence of the isomeric change by way of route (*b*) taking place to any appreciable extent, if at all.

Experimental.

Visnagin (III).—When the initial reaction between visnagone (Späth *et al.*, *loc. cit.*) (1 g.), ethyl acetate (10 ml.), and sodium (1 g.) had subsided, the mixture was heated on the steam-bath for 4 hours with the addition of more acetate (2 ml.) and sodium (1 g., in small portions) after 1 hour. Next day a small amount of unchanged sodium in the reaction mixture was destroyed by addition of a little methanol, and after having been diluted with water (200 ml.) the solution was acidified with acetic acid. Thus precipitated as a brown oil, the product gradually solidified and then on crystallisation from aqueous alcohol gave the 6-*hydroxy*-4-*methoxy*-5-*acetoacetylcoumarone* (II) in colourless platelets (0·35 g.), m. p. 80—81°, which on being dried in a vacuum over phosphoric oxide had m. p. 95—96° [Found, in dried material: C, 62·8; H, 4·7; OMe, 12·1. $C_{12}H_9O_4(OMe)$ requires C, 62·9; H, 4·8; OMe, 12·5%]. This substance, which gives a red ferric reaction in alcohol, is moderately soluble in methanol, warm benzene, or chloroform and readily soluble in acetone or acetic acid.

When a solution of the foregoing diketone (0·25 g.) in alcohol (5 ml.) containing 3 drops of concentrated hydrochloric acid was boiled for 1 minute and cooled, the mixture deposited visnagin, which formed pale yellow prisms (0·2 g.), m. p. 140° from methyl alcohol, undepressed on admixture with an authentic specimen [Found: C, 68·0; H, 4·5; OMe, 13·2. Calc. for $C_{12}H_7O_3(OMe)$: C, 67·9; H, 4·4; OMe, 13·5%]. On being warmed, the yellow solution of the substance in sulphuric acid became orange-red, and then dark red changing to violet on dilution with water. Sodium methoxide (from 0·3 g. of sodium) in methanol (15 ml.) was added to a solution of visnagin (1 g.) and piperonal (1 g.) in methanol (20 ml.), and the mixture heated on the steam-bath for 10 minutes; 48 hours later the solid was collected, washed with a little methanol, and crystallised from dilute acetic acid, giving the *styryl* derivative (1·1 g.) in pale yellow needles, m. p. 220°, sparingly soluble in alcohol, ethyl acetate, or benzene (Found: C, 69·4; H, 4·1. $C_{21}H_{14}O_6$ requires C, 69·6; H, 3·9%).

Ethyl 6-*Hydroxy*-4-*methoxy*-7-*acetylcoumarone*-2-*carboxylate* (V; R = CO_2Et, R_1 = H).—(A) A cooled solution of ethyl 6-hydroxy-4-methoxycoumarone-2-carboxylate (Part IV, *loc. cit.*) (2 g.) in ether (400 ml.), containing acetonitrile (7 ml.) and zinc chloride (3 g.), was slowly saturated with hydrogen chloride and a pale brown oil slowly separated. After the addition of an excess of ether 4 days later, the solvent was decanted and the residual dark red liquid was washed with fresh ether (3 × 50 ml.)

and then dissolved in water (150 ml.). When this solution was almost neutralised (faintly acid to Congo-red paper) with aqueous sodium carbonate, filtered from traces of dark solid, and then heated on the steam-bath for ½ hour, the *ethyl 6-hydroxy-4-methoxy-7-acetylcoumarone-2-carboxylate* gradually separated as a buff-coloured solid (0·5 g.) and on recrystallisation from methanol formed clusters of elongated colourless needles, m. p. 162°, readily soluble in acetone, benzene, or ethyl acetate, and having a violet ferric reaction in alcohol (Found: C, 60·6; H, 5·2. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·1%). On being warmed, the yellow solution of the ketone in sulphuric acid became violet and then red-brown. The 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 295°, from much ethyl acetate (Found: N, 12·0. $C_{20}H_{18}O_9N_4$ requires N, 12·2%).

(B) Powdered aluminium chloride (3 g.) was gradually added during 15 minutes to a suspension of ethyl 6-hydroxy-4-methoxycoumarone-2-carboxylate (2 g.) in nitrobenzene (70 ml.) (agitate) kept at below 5°, and 2 days later the dark red mixture was poured on ice (50 g.). An ethereal solution of the product and nitrobenzene was washed with aqueous sodium hydrogen carbonate to remove hydrochloric acid and then with water, dried, and evaporated on the steam-bath. When the residual nitrobenzene liquor was mixed with an excess of light petroleum (b. p. 60—80°), filtered, and kept at 0° for 16 hours, the ketone (1·6 g.) gradually separated, and on recrystallisation from methanol had m. p. 162°, identical in every way with material prepared by method (A). The 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 295°.

When the light petroleum–nitrobenzene liquors were subjected to distillation in a current of steam a further quantity of ketone (0·15 g.) was isolated from the residual aqueous solution.

An examination of the residues left from the purification of the keto-ester (V; R = CO_2Et, R_1 = H), formed by either method (A) or (B), failed to reveal the presence of the desired isomeride, ethyl 6-hydroxy-4-methoxy-5-acetylcoumarone-2-carboxylate, required for the preparation of visnagone.

6-Hydroxy-4-methoxy-7-acetylcoumarone (iso*Visnagone*) (V, R = R_1 = H).—A solution of the foregoing ketonic ester (1 g.) in aqueous-alcoholic potassium hydroxide (from 1·5 g. of potassium hydroxide, 18 ml. of alcohol, and 12 ml. of water) was refluxed for ¾ hour, cooled, diluted with water (50 ml.), and acidified with dilute hydrochloric acid. Crystallisation of the resulting gelatinous precipitate from warm alcohol gave *6-hydroxy-4-methoxy-7-acetylcoumarone-2-carboxylic acid* (V; R = CO_2H, R_1 = H) in stellate clusters of colourless needles (0·8 g.), m. p. 307—309° (decomp.), moderately soluble in warm alcohol, acetone, or ethyl acetate, and having a purple-red ferric reaction in alcohol [Found: C, 57·8; H, 4·2; OMe, 12·8. $C_{11}H_7O_5(OMe)$ requires C, 57·6; H, 4·0; OMe, 12·4%]. The sulphuric acid reaction of this acid was identical with that of the ethyl ester.

Decarboxylation of the acid (2 g.) was effected with gently boiling quinoline (60 ml.) (oil-bath), containing copper bronze (1 g.), during ½ hour, and a filtered solution of the cooled reaction mixture in much ether was washed with hydrochloric acid and then with aqueous sodium hydrogen carbonate, and then extracted with 8% aqueous sodium hydroxide (40 ml. × 10). Acidification of the combined alkaline extracts gave *6-hydroxy-4-methoxy-7-acetylcoumarone* (V, R = R_1 = H) (1·4 g.), which formed pale yellow rectangular leaflets, m. p. 134—136°, from methanol (charcoal), readily soluble in benzene, acetone, or ethyl acetate and almost insoluble in light petroleum (Found: C, 64·3; H, 5·0. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). This substance gave an emerald-green ferric reaction in alcohol and a yellow solution in sulphuric acid which on being heated became cherry-red, then violet, and finally brown. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in orange-red needles, m. p. 282° (Found: N, 14·5. $C_{17}H_{14}O_7N_4$ requires N, 14·5%).

Decarboxylation of the acid by means of hot glycerol gave a poor yield of the ketone.

7-Methoxy-2-methylfurano(2′ : 3′ : 5 : 6)*chromone* (iso*Visnagin*) (VI, R = Me).—To a solution of the foregoing ketone (0·5 g.) in ethyl acetate (15 ml.) sodium (0·7 g., in small pieces) was gradually added and after the initial reaction had subsided the mixture was heated on the steam-bath for 5 hours; after 3 hours more sodium (0·3 g.) and ester (3 ml.) were added. The cooled reaction mixture was treated with a little methanol to destroy traces of unchanged sodium, diluted with ice-water, and acidified with acetic acid. Next day the *6-hydroxy-4-methoxy-7-acetoacetylchromone* (V; R = H, R_1 = Ac) (0·4 g.) was collected and, after having been sublimed in high vacuum, was crystallised from light petroleum (b. p. 60—80°), forming yellow needles, m. p. 138—139°, soluble in alcohol or benzene and having a green ferric reaction in alcohol (Found: C, 62·9; H, 4·7. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·9%).

A solution of this diketone (0·2 g.) in acetic acid (8 ml.) containing 3 drops of concentrated hydrochloric acid was boiled for 1 minute, cooled, and the *furanochromone* (VI, R = Me) precipitated by the addition of water. Crystallised from alcohol, this compound formed colourless needles, m. p. 247°, and gave a colourless solution in sulphuric acid exhibiting a faint purple fluorescence, unchanged on being warmed (Found: C, 67·6; H, 4·6. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·4%).

6-Hydroxy-4-methoxycoumaran (VII).—The synthesis of this compound, obtained as a low-melting solid, and its characterisation by formation of a *p*-nitrobenzoate, was described in Part IV (*loc. cit.*), the final stage of which was the simultaneous hydrogenation and debenzylation of 6-benzyloxy-4-methoxycoumarone in acetic acid. It has now been found that when this reaction is carried out in methanol with a palladium–charcoal catalyst the product is free from resinous material and can be crystallised from carbon tetrachloride–light petroleum (b. p. 60—80°), forming colourless irregular prisms, m. p. 77° (Found: C, 65·5; H, 6·0. Calc. for $C_9H_{10}O_3$: C, 65·1; H, 6·0%), which gave the *p*-nitrobenzoate, m. p. 159—160°.

6-Hydroxy-4-methoxy-7-acetylcoumaran (VIII, R = H).—(A) Hydrogenation of 6-hydroxy-4-methoxy-7-acetylcoumarone (0·5 g.) in acetic acid (40 ml.) with a palladium–charcoal catalyst (from 0·05 g. of palladium chloride and 0·5 g. of charcoal) was complete in about ½ hour and on isolation the resulting *coumaran* (VIII, R = H) formed pale yellow needles, m. p. 128°, from methanol, readily soluble in benzene or ethyl acetate and moderately soluble in light petroleum, and having an emerald-green ferric reaction in alcohol (Found: C, 63·2; H, 6·1. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%). The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 248°, from ethyl acetate (Found: N, 14·2. $C_{17}H_{16}O_7N_4$ requires N, 14·4%).

(B) Acetyl chloride (0·8 ml.) was added to a well-stirred solution of 6-hydroxy-4-methoxycoumaran (1 g.) in nitrobenzene (50 ml.), maintained at 0°, followed by aluminium chloride (2·4 g., in two portions), the resulting yellow solution (cooled) was agitated for 1 hour, and 2 days later the mixture was treated with ice and extracted with ether. The combined ethereal extracts were washed with aqueous sodium hydrogen carbonate, dried, and evaporated, and the residual liquor mixed with light petroleum (b. p. 60—80°) (250 ml.). Extraction of the latter mixture with 10% aqueous sodium hydroxide (50 ml. × 10) and acidification of the combined extracts with hydrochloric acid gave a ketonic product (0·95 g.), having a dark purple ferric reaction, which on crystallisation from alcohol furnished 6-hydroxy-4-methoxy-7-acetylcoumaran (0·6 g.) in pale yellow needles, m. p. 128°, identical in every way with a specimen prepared by method (A). The 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 248°.

Dihydroisovisnagin (IX).—Interaction of the foregoing ketone (0·45 g.) with ethyl acetate (10 ml.) and sodium (0·6 g.) on the steam-bath for 4½ hours with the addition of more acetate (2 ml.) and sodium (0·2 g.) after 3 hours gave rise to 6-*hydroxy*-4-*methoxy*-7-*acetoacetylcoumaran* (VIII, R = Ac) (0·3 g.), forming clusters of yellow needles, m. p. 135—136°, from light petroleum (b. p. 60—80°) (Found: C, 62·3; H, 5·8. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). This substance is readily soluble in alcohol, acetone, or benzene and has a red-purple ferric reaction in alcohol. A solution of the compound (0·17 g.) in acetic acid (6 ml.) containing 4 drops of concentrated hydrochloric acid was boiled for 2 minutes, cooled, diluted with water, filtered from a trace of brown solid, saturated with ammonium sulphate, and extracted with ether. Evaporation of the washed and dried extracts left the *chromone* (IX) (0·09 g.), which separated from ligroin in tiny colourless prisms, m. p. 193—194° (decomp.) after sintering at 187° (Found: C, 67·0; H, 5·4. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). On being warmed the almost colourless solution of this compound in concentrated sulphuric acid became violet.

Dihydrovisnagone.—Hydrogenation of visnagone (isolated from chellol glucoside; unpublished work) dissolved in acetic acid with a palladium–charcoal catalyst gave the *dihydro*-derivative which separated from methyl alcohol in pale lemon-yellow needles, m. p. 101·5°, readily soluble in ethyl acetate, benzene, or acetone and having a blood-red ferric reaction in alcohol (Found: C, 63·5; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone* formed scarlet needles, m. p. 225°, from ethyl acetate (Found: N, 14·6. $C_{17}H_{16}O_7N_4$ requires N, 14·4%).

4-*Hydroxy*-2 : 6-*dimethoxy*-3-*allylacetophenone.*—A mixture of 4-hydroxy-2 : 6-dimethoxyacetophenone (Curd and Robertson, *J.*, 1931, 1241) (2·5 g.), allyl bromide (2·5 g.), potassium carbonate (6 g.), and acetone (80 ml.) was refluxed for 3½ hours, filtered (wash salts with acetone), and evaporated, leaving the *allyl ether* (2·5 g.) as a crystalline mass. Recrystallised from light petroleum (b. p. 40—60°), the compound formed small prisms, m. p. 56—57°, readily soluble in alcohol, benzene, or ethyl acetate (Found: C, 65·8; H, 7·0. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%). A mixture of this ether (3 g.) and dimethylaniline (20 ml.) was refluxed for 5 hours in an atmosphere of nitrogen, and a solution of the cooled liquor in ether (150 ml.) was washed with dilute hydrochloric acid to remove the base and then extracted with 15% aqueous sodium hydroxide (50 ml. × 6) to remove the resulting *allylphenol*. After acidification of the combined alkaline extracts and subsequent saturation with ammonium sulphate this phenol (2·2 g.) was isolated with ether and crystallised from light petroleum (b. p. 40—60°), forming slender colourless needles, m. p. 71—72°, readily soluble in alcohol or benzene (Found: C, 66·2; H, 7·0. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%). In an attempt to effect the rearrangement in the absence of a solvent (compare Baker and Lothian, *J.*, 1935, 628) the product was an intractable tar.

Acetylation of the allylphenol by the acetic anhydride–pyridine method gave the *acetate*, forming tiny, colourless needles, m. p. 33—34°, from light petroleum (b. p. 40—60°) (Found: C, 64·7; H, 6·5. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%).

Methyl 2 : 6-*Dihydroxy*-4-*methoxy*-3-*formylbenzoate.*—When a mixture of methyl 2 : 6-dihydroxy-4-methoxybenzoate (Herzig and Wenzel, *Monatsh.*, 1901, **22**, 215) (2 g.), hydrogen cyanide (2 ml.), zinc cyanide (2 g.), and ether (150 ml.) was saturated with hydrogen chloride the aldimine began to separate in the course of 1 hour. After the addition of excess ether next day, the product was collected, washed with ether to remove excess of hydrogen chloride, and dissolved in water (150 ml.). Aqueous sodium hydrogen carbonate was added until the solution was only faintly acid to Congo-red, and the mixture heated on the steam-bath for 15 minutes. Next day the resulting *aldehyde* (2 g.) was collected, and crystallised from alcohol (charcoal), forming elongated silky, colourless needles, m. p. 177·5°, having a blood-red ferric reaction in alcohol (Found: C, 52·8; H, 4·4. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·4%). The *semicarbazone* separated from acetic acid in pale yellow needles, m. p. 230° (Found: N, 14·7. $C_{11}H_{13}O_6N_3$ requires N, 14·8%).

Condensation of the same ester (5 g.) with acetonitrile (12 ml.) in ether (150 ml.) by means of zinc chloride (5 g.) and excess of hydrogen chloride according to Hoesch's method gave rise to a semi-solid ketimine which on hydrolysis with water (200 ml.) on the steam-bath for 20 minutes furnished *methyl* 2 : 6-*dihydroxy*-4-*methoxy*-3-*acetylbenzoate* (1·9 g.), forming colourless needles, m. p. 144°, from alcohol (Found: C, 55·2; H, 5·1. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%). This ketone gave a reddish-brown ferric reaction in alcohol and formed a 2 : 4-*dinitrophenylhydrazone* which separated from ethyl acetate in orange needles, m. p. 212—213° (Found: N, 13·5. $C_{17}H_{14}O_9N_4$ requires N, 13·3%). Unchanged ester (3 g.) was recovered from the ethereal liquors decanted from the ketimine. The use of a smaller proportion of acetonitrile in the reaction mixture led to poorer yields of ketone.

Demethylation of Visnagin.—Acetic anhydride (20 ml.) was carefully added to concentrated hydriodic acid (14 ml.) containing visnagin (2 g.), and the mixture gently refluxed (oil-bath) for 30 minutes. The cooled dark red solution was diluted with water (200 ml.) containing a little sodium hydrogen sulphite to remove traces of free iodine, and the pale yellow flocculent precipitate was collected and washed with water and then with a little methanol. Crystallised from dilute acetic acid, this product (0·4 g.) gave 7-*hydroxy*-2-*methylfurano*(2′ : 3′ : 5 : 6)*chromone* (VI, R = H) as a *hydrate* in almost colourless prisms, m. p. 318° (decomp.), which have a very faint green ferric reaction in alcohol and are sparingly soluble in methanol, alcohol, or acetone (Found, in material dried in a vacuum at room temperature: C, 61·1; H, 4·3. $C_{12}H_8O_4,H_2O$ requires C, 61·5; H, 4·3%. Found, in material dried at 120° for 2 hours: C, 66·6; H, 3·8. $C_{12}H_8O_4$ requires C, 66·7; H, 3·7%).

A mixture of this compound (0·25 g.), potassium carbonate (1 g.), acetone (30 ml.), and methyl iodide (2 ml.) was refluxed for 16 hours, filtered, evaporated, and the pale brown residual solid crystallised from dilute methanol, giving *iso*visnagin in almost colourless slender prisms (0·2 g.), m. p. 247°, identical in every way with a specimen obtained by direct synthesis (Found: C, 68·1; H, 4·6%). Interaction of this material (0·1 g.) with piperonal (0·1 g.) in 6% methanolic sodium methoxide on the steam-bath during 1½ hours gave rise to the *styryl* derivative of *iso*visnagin, which formed slender yellow needles, m.p. 244°, from dilute acetic acid and was identical with a specimen, m. p. 244°, prepared in the same manner from synthetical *iso*visnagin (Found: C, 69·3; H, 3·7. $C_{21}H_{14}O_6$ requires C, 69·5; H, 3·9%). When *iso*visnagin (0·1 g.), prepared from visnagin by the hydriodic acid method, was refluxed with 20% aqueous potassium hydroxide (20 ml.) for 1 hour, and the cooled solution acidified with acetic acid, a bulky white precipitate separated. On crystallisation from methanol this product gave *iso*visnagone (50 mg.) in pale yellow rectangular platelets, m. p. 134°, identical in every way with a synthetical specimen.

Addition of water to the methanol washings of the crude demethylation product and to the dilute acetic acid liquors left on purification of (VI, R = H) gave a small amount of an alkali-soluble powder which had a dark green ferric reaction in alcohol, changing to dull purple on dilution with water and which may contain norvisnagin or the isomeride (XII). So far all attempts to obtain a crystalline compound from this material have been unsuccessful. Methylation of the crude product by the methyl iodide–potassium carbonate method yielded an amorphous powder which was insoluble in aqueous alkali and had a negative ferric reaction but a definite compound could not be isolated.

The authors are indebted to Messrs. Imperial Chemical Industries Limited for a grant in aid of this work.

UNIVERSITY OF LIVERPOOL. [*Received, January 29th,* 1948.]

---

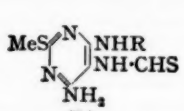
459. *Infra-red Spectroscopic Measurements of Substituted Pyrimidines. Part I. The Presence of Hydrogen Bonding in 4-Triacetyl-D-xylosidaminopyrimidines.*

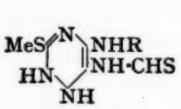
By I. A. BROWNLIE, G. B. B. M. SUTHERLAND, and A. R. TODD.

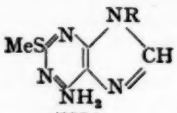
Infra-red methods have been used to demonstrate the presence of hydrogen bonding in certain 4-triacetyl-D-glycosidaminopyrimidines; the results substantiate a chelation hypothesis previously put forward on chemical evidence (Kenner, Lythgoe, and Todd, *J.*, 1944, 652; 1946, 852; Howard, Lythgoe, and Todd, *J.*, 1945, 556). Where hydrogen bonding is absent, the band due to the stretching vibration of the acetoxy >C=O groups is centred at 1750 cm.$^{-1}$, but where the C′$_2$ acetoxy-carbonyl is bonded to the glycosidic NH group, an additional >C=O band at 1725 cm.$^{-1}$ is present.

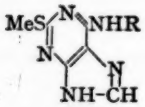
FOLLOWING the demonstration by Baddiley, Lythgoe, McNeil, and Todd (*J.*, 1943, 383) that cyclisation of 6-amino-4-methylamino-5-thioformamidopyrimidines, *e.g.* (I; R = Me), yielded exclusively the corresponding 9-methyladenines, unaccompanied by 6-methylaminopurines, a general method for the synthesis of 9-glycosidoadenine derivatives was developed, involving as a final stage, cyclisation of 6-amino-4-glycosidamino-5-thioformamidopyrimidines it being assumed that the glycosidic residue could be regarded as analogous to the methyl group in the above model experiments. It was suggested that the thioformamido-compounds exist in form (II; R = Me or glycosido) and that, accordingly, base-catalysed ring closure would not readily proceed by intervention of the imino-group at position 6. Application of this synthetic method has led to the successful synthesis of a variety of 9-glycosidoadenine derivatives, but the expectation that these would be the sole products has not been invariably fulfilled. Kenner and Todd (*J.*, 1946, 852) have reviewed a number of these cases and discussed the mechanism of the final cyclisation process in detail. Briefly, it has been found that, whereas 6-amino-4-glycosidamino-5-thioformamidopyrimidines do in fact behave like the 4-alkylamino-compounds and yield only 9-glycosidopurines, the corresponding acetylated glycosides normally give a mixture of 9-glycosidoadenine and 6-glycosidaminopurine derivatives on cyclisation. To quote a specific example, cyclisation of 6-amino-4-D-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine (I; R = D-xylosido) gives only 9-D-xylopyranosido-2-methylthioadenine (III; R = D-xylosido), whereas the corresponding triacetylthioformamidoglycoside (I; R = triacetyl-D-xylosido) cyclised under conditions which prevent deacetylation gives a mixture of the 9-glycoside (III; R = triacetyl-D-xylosido) and 6-triacetyl-*d*-xylopyranosidamino-2-methylthiopurine (IV; R = triacetyl-D-xylosido) (Howard, Lythgoe, and Todd, *J.*, 1945, 556). To explain these results, it was postulated (Kenner, Lythgoe, and Todd, *J.*, 1944, 652; Howard, Lythgoe, and Todd, *loc. cit.*; Kenner and Todd, *loc. cit.*) that a chelate ring may be formed in acetylated 4-glycosidaminopyrimidines as shown in (V) through a hydrogen bond between the

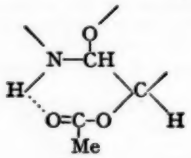
2-acetyl group in the sugar residue and the hydrogen atom of the glycosidic NH-group. The effect of such chelation would be to induce negative charge on the glycosidic nitrogen atom, thus increasing its basicity and also indirectly that of the nitrogen attached to position 6. As a result, the reactivity of the whole molecule would be increased and cyclisation might occur in either direction, to give an acetylated 9-glycosidoadenine or an acetylated 6-glycosidamino-purine. This hypothesis accorded well with the observed facts but was not readily susceptible of proof by chemical methods.


(I.)


(II.)


(III.)


(IV.)


(V.)

The same hypothesis was used by Howard, Kenner, Lythgoe, and Todd (*J.*, 1946, 855) to explain certain interconversion reactions of 4-glycosidaminopyrimidines. Whereas, for example, the α- and β-isomers of 5-nitroso-6-amino-4-D-xylopyranosidamino-2-methylthiopyrimidine are stable and do not show mutarotation, acetylation of either gives rise to one and the same triacetyl derivative; it was suggested by these authors that the increased basicity of the glycosidic nitrogen in the acetylated compounds so facilitates configurational change at the glycosidic carbon that as a result one of the acetylated nitroso-compounds undergoes a rapid and complete mutarotation to its more stable isomer.

The present investigation was undertaken in order to determine by infra-red spectroscopy whether hydrogen bonding of the type postulated could be detected in suitable acetylated 4-glycosidamino-pyrimidines.

There are at least two ways in which the formation of such a hydrogen bond might be expected to affect the vibration spectrum of compounds of this type. The weak link between the oxygen of the CO group and the hydrogen of the NH group should (*a*) cause a lowering of the C=O stretching frequency, normally near 1760 cm.$^{-1}$, similar to that found in the carboxylic acids by association (Davies and Sutherland, *J. Chem. Physics*, 1938, **6**, 767) and (*b*) produce a corresponding lowering of the NH stretching frequency normally near 3400 cm.$^{-1}$. It might also be expected to increase the NH deformation frequency, but as the location of this frequency is not so well established, we decided to concentrate our attention on the first two effects. The general method was to compare the spectra of compounds in which hydrogen bonds were suspected to exist with those of the nearest analogue in which a hydrogen bond could be definitely excluded.

Experimental.

Since substituted 4-D-glycosidaminopyrimidines are, in general, soluble only in solvents which absorb strongly in the region 2 μ (5000 cm.$^{-1}$) to 15 μ (667 cm.$^{-1}$), they were examined as a capillary layer, between rock-salt plates, as a fine suspension in "Nujol." As the work formed part of a larger programme, the substances were examined from 2 to 15 μ on a double-beam spectrometer (Sutherland and Thompson, *Trans. Faraday Soc.*, 1945, **41**, 174) fitted with a 30° rock-salt prism of the Littrow type and a Hilger–Schwarz vacuum thermopile. The compounds were further examined from 2 to 6 μ on a special spectrometer of very high resolving power (cf. Sutherland, Blackwell, and Fellgett, *Nature*, 1946, **158**, 873) fitted with a lithium fluoride prism.

Results and Discussion.—The results for the region of the C=O stretching frequency are summarised in the table and illustrated in Figs. 1—5; the complete results for the region 2—15 μ will appear in a further paper on a series of substituted pyrimidines (Brownlie and Sutherland, in preparation). The evidence obtained from the 3 μ region was not clear-cut, since the absorption frequency of the glycosidic NH group is complicated by the absorption of other substituents in the pyrimidine ring, especially that due to the NH_2 group. The full discussion of the region is reserved for the comprehensive paper.

The double-bond region of the spectrum of 5-nitroso-6-amino-4-D-xylosidamino-2-methylthiopyrimidine is shown in Fig. 1, together with the spectrum of the corresponding triacetyl derivative. The bands between 1650 and 1500 cm.$^{-1}$ are known not to be due to CO groups and may be ignored; the absorption due to CO groups which appears only for the latter compound is seen to consist of a double band, the stronger component being at 1760 cm.$^{-1}$ and the weaker at 1725 cm.$^{-1}$. The former we assign to the C=O groups on the C_3 and C_4 atom of D-xylose, while the latter (being at a lower frequency) we assign

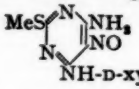
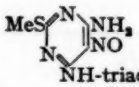
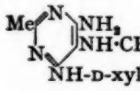
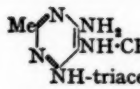
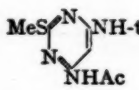
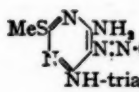
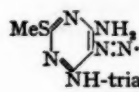
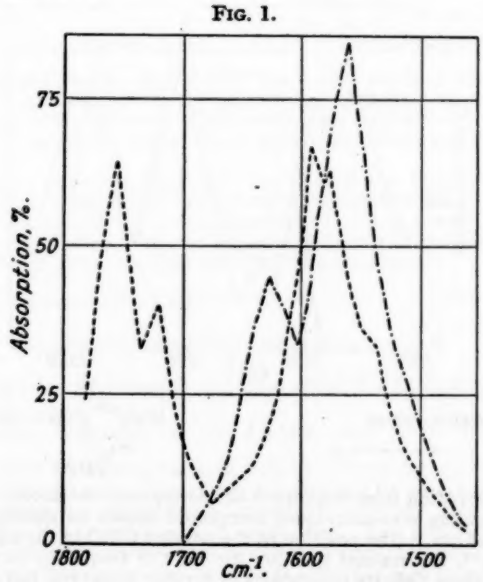
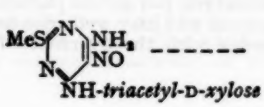
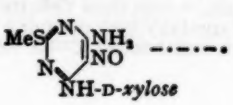
Compound.	Fig.	Remarks.
 NH-D-xylose	1	No bands between 1650 and 1775 cm.$^{-1}$.
 NH-triacetyl-D-xylose	1	One band at 1775 cm.$^{-1}$ due to >C=O stretching frequency of the OAc groups at C_3 and C_4 of D-xylose. One band at 1725 cm.$^{-1}$ due to bonded >C=O at C_2.
1: 2 : 3 : 4-Tetra-acetyl D-xylose	2	One broad band at 1750 cm.$^{-1}$ due to >C=O stretching vibration frequency.
 NH-D-xylose	3	No bands 1700—1775 cm.$^{-1}$.
 NH-triacetyl-D-xylose	3	One band at 1750 cm.$^{-1}$ due to >C=O stretching frequency of the OAc groups at C_3 and C_4 of D-xylose. One band at 1725 cm.$^{-1}$ due to bonded >C=O at C_2.
NHAc	4	One band at 1695 cm.$^{-1}$ due to >C=O frequency of the 6-NHAc group.
 NHAc	4	One band at 1745 cm.$^{-1}$ due to >C=O stretching frequency of the OAc groups at C_3 and C_4 of D-xylose. One band at 1710 cm.$^{-1}$ probably due to bonded >C=O at C_2, overlapping >C=O absorption frequency of the 6-NHAc group.
 NH-triacetyl-D-ribopyranose	5	One band at 1755 cm.$^{-1}$ due to >C=O stretching frequency of the OAc groups. No shifted >C=O frequency present.
 NH-triacetyl-L-arabopyranose	5	One band at 1750 cm.$^{-1}$ due to >C=O stretching frequency. No shifted C=O frequency present.

FIG. 1.



 NH-*triacetyl*-D-*xylose* ------

 NH-D-*xylose* -·-·-·

to the C=O which is bonded to the glycosidic NH group. It might be argued that the splitting does not arise from the existence of the bonded C=O group but is due to resonance between the three C=O frequencies. That this is most unlikely is proved by the spectrum of 1 : 2 : 3 : 4-tetra-acetyl D-xylose (Fig. 2) which shows a single C=O absorption band centred at 1750 cm.$^{-1}$.

FIG. 2.

1 : 2 : 3 : 4-*Tetra-acetyl* D-*xylose*.

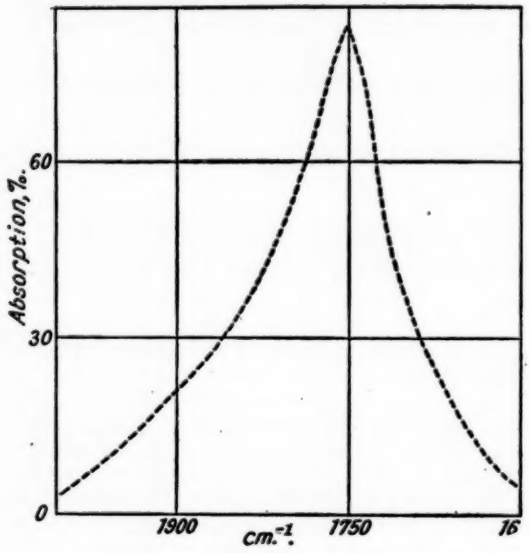
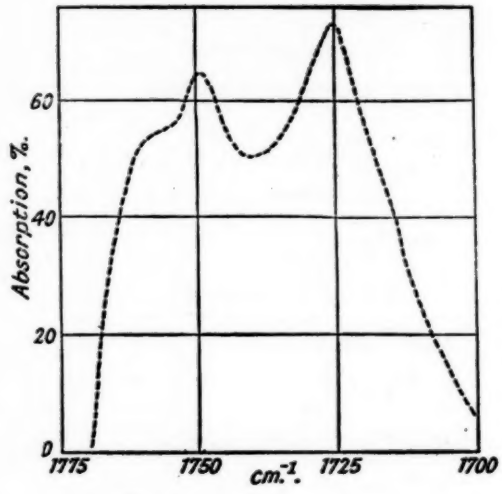
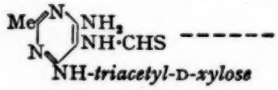
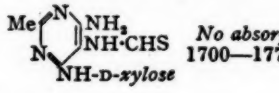


FIG. 3.

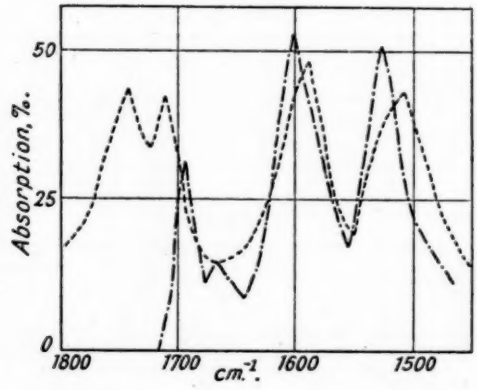


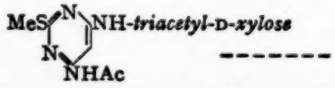




No absorption, 1700—1775 *cm.*$^{-1}$.

FIG. 4.





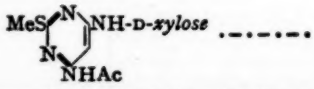
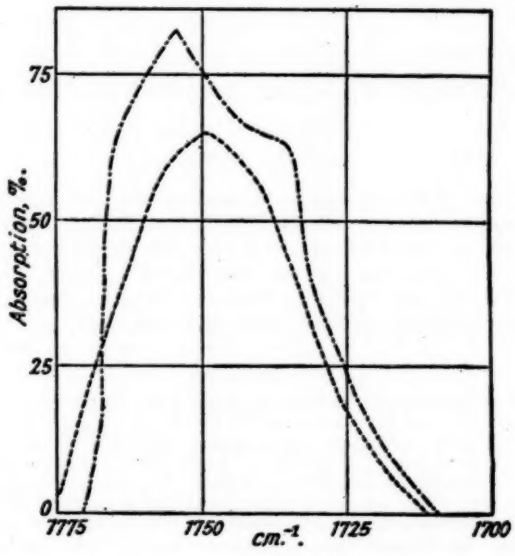


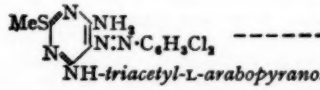
Fig. 3 shows the CO absorption from 6-amino-5-thioformamido-4-triacetyl-D-xylosidamino-2-methylpyrimidine. The corresponding non-acetylated compound shows no absorption in this region. Here again we find a band at 1725 cm.$^{-1}$ (the position of the bonded C=O in the analogous nitroso-compound) and a band near 1750 cm.$^{-1}$, the normal position for the CO frequency in an acetylated sugar. The band near 1750 cm.$^{-1}$ does show definite indications of further structure, but as this particular band was examined under specially high resolving power, this is not unexpected and may well arise from resonance between the two non-bonded C=O vibrations or even resonance with the overtone of some lower frequency.

The comparison between the spectrum of 6-acetamido-4-D-xylosidamino-2-methylthiopyrimidine and that of the corresponding triacetylated compound is given in Fig. 4. The former shows a band at 1695 cm.$^{-1}$, which by comparison with the spectra of other pyrimidines (not shown here) must be due to the C=O bond of the 6-acetamido-group. The latter shows a double band with maxima at 1745 cm.$^{-1}$ and 1710 cm.$^{-1}$. The band at 1745 cm.$^{-1}$ again corresponds to the position for non-bonded acetyl C=O groups in the other molecules, while the maximum at 1710 cm.$^{-1}$ may reasonably be presumed to arise from an overlapping of a bonded C=O frequency at 1725 cm.$^{-1}$ with the acetamido C=O frequency at 1695 cm.$^{-1}$.

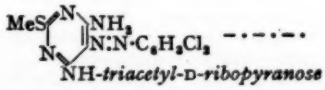
Finally in Fig. 5 are given the C=O absorption bands found in 6-amino-4-triacetyl-D-ribopyranosamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine and the corresponding L-arabopyranose compound. Here we find in each case one strong band (with a few signs of structure) centred at 1750 cm.$^{-1}$

FIG. 5.





NH-*triacetyl*-L-*arabopyranose*



NH-*triacetyl*-D-*ribopyranose*

and no trace of any absorption near or below 1725 cm.$^{-1}$ (the position where a bonded CO might be expected). The absence of any evidence for hydrogen bonding in the triacetyl-5-arylazoglycosides is of considerable interest in view of its presence in the analogous 5-nitroso-compounds. This is in accord with the observed fact that, unlike the latter, the triacetyl-5-arylazoglycosides are capable of existence in both α- and β-forms.

Thus in every case where chemical behaviour has caused the introduction of the hypothesis of hydrogen bonding, a band has been found in the neighbourhood of 1710—1725 cm.$^{-1}$, whereas when chemical evidence was against chelation a single absorption has been found near 1750 cm.$^{-1}$, the normal position for an acetylated sugar. The infra-red evidence in favour of the original hypothesis of Kenner, Lythgoe, and Todd may therefore be regarded as virtually conclusive.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 11th*, 1948].

---

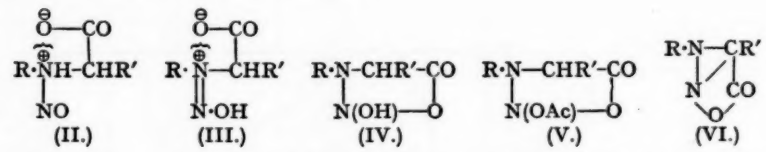
460. *The Dipole Moments of* N- *and* C-*Substituted Sydnones.*

By J. C. EARL, ELEANOR M. W. LEAKE, and R. J. W. LE FÈVRE.

The dipole moments of seven selected sydnones have been determined in benzene solution at 25° by the refractivity method. The values obtained all lie within the range 5—7 D. The "sydnone" skeleton seems to contribute a component moment between 5 and 6 D. acting *approximately* along the R→N bond axis in each case. The measurements are discussed relatively to the possibilities of mesomerism in this and certain other series.

Data for *N*-nitrosophenylglycine and its benzyl ester are also included. The former does not appear to be a "zwitterion." Their two moments have magnitudes to be expected for an acid and its ester. No clear decision can, however, be made between the open-chain or a hydroxy-lactone formulation for nitrosophenylglycine.

During the past twelve years, Earl and his collaborators (*J.*, 1935, 899; 1946, 591) have prepared a range of "sydnones" by the treatment of variously substituted *N*-nitroso-*N*-alkyl- or -aryl-glycines with acetic anhydride. Neither the structures of these new substances (cf. Earl *et al.*, *loc. cit.*; *Nature*, 1946, **158**, 909; Baker and Ollis, *ibid.*, p. 703; Kenner and Mackay, *ibid.*, p. 909) nor the mechanisms underlying their formation are yet decided. Earl and Mackney (*loc. cit.*, 1935) have demonstrated that the apparent overall reaction is only the removal of the elements of water from nitroso-acids, whose formulations are themselves in doubt, since they may be free acids (I), zwitterions such as (II) or (III), or hydroxy-lactones of types shown by (IV). Earl and Mackney raised the possibility that (IV) or its acetyl derivative (V) might precede the isolable "sydnones," which were formulated tentatively as (VI) (*i.e.*, as lactones of 2-hydroxy-1-substituted-diaziridine-3-carboxylic acids).



(I.) (II.) (III.) (IV.) (V.) (VI.)

Two problems therefore exist: (*a*) Are the initial substances (I), (II), (III), (IV), or (V)? (*b*) Are the sydnones adequately represented as (VI), and if not, what are preferable alternatives? In this paper we record attempts to investigate these questions by dipole-moment measurements. During the work we learned that, independently, similar projects were in hand by Dr. Sutton at Oxford and Professor Baker at Bristol. Preliminary results from the three groups have already appeared (*Nature*, 1947, **160**, 366, 367).

Experimental.

The dielectric-constant measurements have been made with the simple 1 Mc. oscillator described by Le Fèvre and Calderbank (this vol., p. 1950), and the total molecular polarisations at infinite dilution evaluated by the equation $\infty P_T = M[p_2(1 - \beta) + C\alpha\epsilon_2]$, where M = molecular weight of solute, $p_2 = (\epsilon_2 - 1)/(\epsilon_2 + 2)d_2$, and $C = 3/d_2(\epsilon_2 + 2)^2$ (cf. *J.*, 1937, 1805). The suffix 2 refers to the solvent, benzene, for which we take $\epsilon_2 = 2{\cdot}2725$ and $d_4^{25°} = 0{\cdot}87378$. Our determinations (all at 25°) have been made relatively to these figures. For the earlier experiments we were compelled to use a Sayce–Briscoe type cell of *ca.* 35 $\mu\mu$F. air capacity in conjunction with the vernier of a 50—250 $\mu\mu$F. Sullivan variable air condenser. Observations so obtained are asterisked. Later, a cell of 93 $\mu\mu$F. air capacity was substituted and a revolution counter (reading to 0·01 turn, *i.e.*, *ca.* 0·007 $\mu\mu$F.) fitted to the driving shaft of the Sullivan condenser. Both accuracy and ease of reading were thus made greater.

The solutes used were: *N*-nitrosophenylglycine, m. p. 101·5° (decomp.) (Earl and Mackney, *loc. cit.*, give m. p. 102—103°; *N*-nitrosophenylglycine benzyl ester, m. p. 55·5—56·5° (unpublished observation by Mr. J. Delmenico); *N*-phenylsydnone, m. p. 133—134° (Earl and Mackney give 134—134·5°); *N*-*p*-bromophenylsydnone, m. p. 138—139° (Eade and Earl, this vol., p. 2307, give 137·5—138·5°); *N*-phenyl-*C*-methylsydnone, m. p. 98—99° (Earl and Mackney give 98—99°); *C*-bromo-*N*-phenylsydnone, m. p. 133—134° (decomp.) (Kenner and Mackay, *loc. cit.*, give 134°); *NC*-diphenylsydnone, m. p. 184—185° (Eade and Earl give 184—185°); *N*-benzylsydnone, m. p. 66·5—67·5° (Baker, Sutton, *et al.*, *locc. cit.*, give 70°; Eade and Earl, 68—69°); *N*-β-naphthylsydnone, m. p. 161—162° (Eade and Earl give 159°, decomp.).

As solvent for the dielectric-constant and density measurements (Table I), A.R. benzene, dried over sodium wire, was fractionally crystallised, one-third rejected, and the melted residue stored over sodium. For the refractivities, however, the solubilities of the sydnones were found to be too low in benzene for accurate observations on the Abbé refractometer available. Solutions of *N*-phenyl- and *N*-β-naphthyl-sydnones in redistilled *cyclo*hexanone were therefore used at concentrations of 3—5%. The $[R_L]_D$ values for the remaining sydnones (Table III) were calculated from the results (Table II) so obtained.

Apart from the above points, experimental procedures have been those described by Le Fèvre ("Dipole Moments," Methuen, 2nd Edn., Chap. II). The symbols used in the following tables have their usual significance (cf., *e.g.*, *J.*, 1937, 1805).

In the discussion below reference is made to the effect of dissolved *N*-nitrosophenylglycine on the dielectric constant of water or alcohol. Our experiments on these points have been made using a small concentric cylindrical condenser, of about 2 $\mu\mu$F. air capacity, constructed similarly (except for size) to that illustrated in *Trans. Faraday Soc.*, 1938, **34**, 1128, Fig. 2. This was rigidly clamped by its earthed lead and immersed to constant depth in the solvent under examination; from it, a coaxial cable connection ran to the oscillator used above, and was attached in place of the lead to the thermostat, cell, etc.

The procedure was as follows: With conductivity water or absolute alcohol as dielectric, and the milliammeter indicating that the quartz crystal was only just resonating (the most sensitive setting), the vernier reading on the Sullivan condenser was noted. Small amounts of the solute were then stirred into solution without disturbing any of the components, and a new setting of the variable condenser found which would restore the original current. An increase of the measured capacity showed that $\epsilon_{solution}$ was less than $\epsilon_{solvent}$ and *vice versa*. The room temperature was steady at 28° throughout.

TABLE I.

100 w_1.	$\epsilon^{t°}$.	$d_4^{t°}$.	$d\epsilon_2$.	βd_2.
0·0000	2·2725	0·87378	—	—
	N-*Nitrosophenylglycine.*			
0·3745	2·2973	0·87486	6·62	0·288
0·4438	2·3012	0·87508	6·47	0·293
0·4546	2·3015	—	6·38	—
0·4797	2·3033	0·87515	6·42	0·286
0·5316	—	0·87528	—	0·282
	N-*Nitrosophenylglycine benzyl ester.*			
1·6890	2·3883	0·87756	6·86	0·224
2·2725	2·4282	0·87887	6·85	0·224
2·5780	2·4498	0·87959	6·87	0·225
	N-*Phenylsydnone.*			
0·3196	2·3691 *	0·87485	30·23	0·335
0·4546	2·4017	—	28·42	—
0·5294	2·4360 *	0·87551	30·88	0·327
0·5668	2·4322	—	28·18	—
0·5884	2·4424	0·87570	28·87	0·326
0·6023	2·4433	0·87571	28·36	0·324
0·6843	2·4658	—	28·25	—
0·7124	2·4754 *	0·87612	28·48	0·329
	N-*Benzylsydnone.*			
1·1470	2·5389 *	0·87720	23·23	0·298
1·7650	2·6823 *	0·87910	23·22	0·301
0·4499	2·3270	0·87585	12·11	0·460
0·45365	2·3285	0·87586	12·34	0·459
0·6588	2·3530	0·87678	12·22	0·455
0·8263	—	0·87756	—	0·457
1·1169	—	0·87892	—	0·460
	N-*Phenyl*-C-*methylsydnone.*			
0·6812	2·4611 *	—	27·70	—
1·0620	2·5645 *	0·87697	27·50	0·300
1·5520	2·6902 *	0·87836	26·91	0·295
	C-*Bromo*-N-*phenylsydnone.*			
0·2755	2·3256 *	0·87504	19·3	0·457
0·4752	2·3696 *	0·87590	20·4	0·446
0·8859	2·4391 *	0·87774	18·8	0·447
	NC-*Diphenylsydnone.*			
0·2261	2·3190 *	0·87434	20·57	0·248
0·3593	2·3458 *	0·87473	20·40	0·264
0·4855	2·3681 *	0·87512	19·69	0·276
	N-*β-Naphthylsydnone.*			
0·2500	2·3367 *	0·87459	25·68	0·324
0·3163	2·3515 *	0·87483	24·98	0·332
0·3643	2·3624 *	0·87596	24·68	0·324

TABLE II.

Molecular refractions.

100 w_1.	$d_4^{25°}$.	$n_D^{25°}$.	r_{12}.	$[R_L]_D$.	100 w_1.	$d_4^{25°}$.	$n_D^{25°}$.	r_{12}.	$[R_L]_D$.
	N-*Nitrosophenylglycine benzyl ester in benzene.*								
0·0000	0·8738	1·5095	0·3421	—	2·5788	0·8796	1·5120	0·3411	81·9
2·2725	0·8789	1·5116	0·3412	81·6					
	N-*Phenylsydnone in* cyclo*hexanone.*								
0·0000	0·94110	1·4502	0·28567	—	4·866	0·95466	1·4569	0·28522	45·9
	N-*β-Naphthylsydnone in* cyclo*hexanone.*								
0·0000	0·94111	1·4509	0·28599	—	3·568	0·95110	1·4570	0·28689	66·0

TABLE III.

Results calculated from mean α and β values.

Substance.	$\alpha\epsilon_2$.	βd_2.	$[R_L]_D$, c.c.	P_1, c.c.	μ, D.
N-Nitrosophenylglycine	6·47	0·287	53	260	3·18
N-Nitrosophenylglycine benzyl ester	6·86	0·224	81·7	417·3	4·06
Sydnones:					
N-Phenyl-	28·96	0·328	45·9	917	6·53
N-p-bromophenyl-	12·22	0·458	53·8	593	5·13
* *N*-Phenyl-*C*-methyl-	27·37	0·297	50·5	946	6·6
* *C*-Bromo-*N*-phenyl-	19·5	0·450	53·8	923	6·5
* *NC*-Diphenyl-	20·22	0·262	69·9	963	6·6
* *N*-Benzyl-	23·22	0·299	50·5	808	6·1
* *N-β*-Naphthyl-	25·1	0·326	66·0	1045	6·9

For comparison, we include data recently received (private communication) from Dr. Sutton, together with (in parentheses) the moments reported earlier by Baker, Ollis, Poole, Barltrop, Hill, and Sutton (*Nature*, 1947, *loc. cit.*):

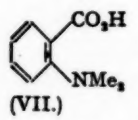
	μ, D.		μ, D.
N-Phenylsydnone	6·47 (6·50)	*N*-Benzylsydnone	6·28
N-p-Tolylsydnone	6·86 (6·93)	*C*-Bromo-*N*-phenylsydnone	6·42
N-p-Chlorophenylsydnone	5·00 (5·04)	*N*-Phenyl-*C*-methylsydnone	6·56
*N-cyclo*Hexylsydnone	6·70 (6·62)	*NC*-Diphenylsydnone	6·62

N-Nitrosophenylglycine was thus found to *lower* the dielectric constants of both water and alcohol, but to a less degree than did aniline and acetanilide. With acetamide the diminution was slight but observable. We view this last fact as justifying our conclusions (see below), although observations were only made qualitatively. As a further check we examined successively specimens of chloroform, ether, chlorobenzene, acetone, and nitrobenzene, and plotted condenser readings against dielectric constants. From the resulting curve our settings for absolute alcohol and conductivity water corresponded to $\epsilon = 23{\cdot}8$ and $77{\cdot}4$, respectively, in good agreement with accepted modern values (Åkerlöf, *J. Amer. Chem. Soc.*, 1932, **54**, 4125; Jones and Davies, *Phil. Mag.*, 1939, **28**, 307).

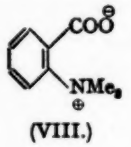
Discussion.

The measurements now reported indicate that *N*-nitrosophenylglycine lacks the polarity of the true zwitterions. The actual dipole moments of such molecules, although never yet *directly* measured, have been deduced from the alterations of dielectric constants of polar solvents which follow the addition of zwitterionic solute, the relevant observations being commonly expressed as the ratio $\Delta\epsilon/\Delta c$ per mole. Thus the series $\overset{+}{N}H_3{\cdot}[CH_2]_n{\cdot}C\overset{-}{O}O$ has $\Delta\epsilon/\Delta c = +26$, $+35$, $+52$, $+70$, $+73$, $+86$ per mole for $n = 1$ to 6 respectively (Wyman, *Chem. Reviews*, 1936, **19**, 213). It is relevant to note that phenylglycine itself shows $\Delta\epsilon/\Delta c =$ *ca.* 30 per mole (Devoto, *Gazzetta*, 1934, **64**, 371). These figures refer to solutions in water. The contrast with similar data for substances soluble in both water and benzene is important. Thus aniline, $\mu = 1{\cdot}5$ D. in benzene, has $\Delta\epsilon/\Delta c = -7{\cdot}6$ per mole in water, while for phenol, acetamide, *s*-dimethylurea, and dimethylanthranilic acid (VII) the corresponding data are $1{\cdot}6 : -6{\cdot}6$, $3{\cdot}6 : -0{\cdot}8$, $4{\cdot}8 : +3{\cdot}0$, $6{\cdot}3 : 12$—17 (Wyman, *loc. cit.*). The comparison of (VII) with *o*-benzbetaine (VIII; $\Delta\epsilon/\Delta c = 19$ or 20, Devoto, *loc. cit.*; Edsall and Wyman, *J. Amer. Chem. Soc.*, 1935, **57**, 1964) suggests that (VII) is not fully dipolar.

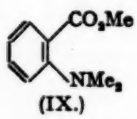
Wyman (*ibid.*, 1934, **56**, 536; 1936, **58**, 1482) and Kuhn (*Z. physikal. Chem.*, 1935, **175**, *A*, 1) conclude from the rough proportionality between $\Delta\epsilon/\Delta c$ and molar polarisation that μ_{glycine} is about 12 D., *i.e.*, close to the value to be expected on elementary theory.



(VII.)



(VIII.)



(IX.)

The examples (VII) and (VIII) are especially mentioned since in conjunction with (IX) they illustrate another test for a zwitterionic structure of nitrosophenylglycine.

The methyl ester (IX) isomeric with (VIII) has $\mu = 2{\cdot}05$ D. in benzene (Wyman, *loc. cit.*; Wyman and McMeekin, *J. Amer. Chem. Soc.*, 1933, **55**, 915) in common with other amino-acid esters. From nitrosophenylglycine to its benzyl ester, however, we find no diminution of moment, but instead an *increase* of 0·9 D.—a change in the expected direction for a normal acid–ester relationship (*e.g.*, $CH_3{\cdot}CO_2H$, 1·7; $CH_3{\cdot}CO_2Ph$, 1·9; $Ph{\cdot}CO_2H$, 1·0; $Ph{\cdot}CO_2{\cdot}CH_2Ph$, 1·9—2·1, cf. *Trans. Faraday Soc.*, 1934, Appendix) and quite contrary to that inferred for the amino-acid and ester pairs, and dimethylanthranilic acid and its methyl ester, cited above.

We conclude therefore that formulæ of the types (II) and (III) contribute negligibly to the real structure of *N*-nitrosophenylglycine and may be eliminated.

No decision between (I) and (IV) is possible on available evidence, since the moments now found for the acid and its benzyl ester both fall between the extreme values which may be forecast for various configurations of (I) or (IV) by the application of link moments (Eucken and Meyer, *Physikal. Z.*, 1929, **30**, 397) to reasonably assumable scale models.

Turning now to the sydnones themselves (Table III), it is seen that the ten examples, for which data are now provided, have moments between 5 and 7 D. If, throughout all sydnones, there is a fixed and recurrent " nucleus " of atoms, then likewise there should be a fixed and recurrent " nucleus " moment, which, compounded with appropriate substituent link moments, should enable the observed value for any member to be calculated from that for its unsubstituted parent. *Very roughly* this does seem to be the case for the *N*-phenylsydnones, since, taking $\mu C \rightarrow$ halogen as 1·55 D. and $\mu C \leftarrow$ Me as 0·4 D., angles of interaction, θ, are calculable from Table III as follows :

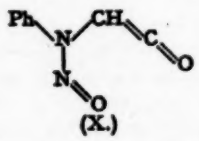
Substance.	θ.	Angles between lines of action.*
C-Bromo-*N*-phenylsydnone	98°	98°
N-Phenyl-*C*-methylsydnone	82	98
N-*p*-Tolylsydnone	13	167
N-*p*-Chlorophenylsydnone	164	164
N-*p*-Bromophenylsydnone	158	158

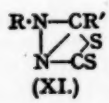
* Measured anticlockwise from the direction of action of the *N*-phenylsydnone moment.

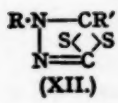
It is therefore obvious that, as stated by Sutton *et al.* (*Nature, loc. cit.*), the moment of *N*-phenylsydnone can be viewed as operative in derived molecules and acting within 20° to the Ph–N bond, with its negative pole directed *away*, through the N atom, from the substituent. It will be noted also that from the *p*-bromo- to the *C*-bromo-member there is a θ difference of *ca.* 60°, and from the *p*-methyl- to the *C*-methyl-, one of *ca.* 70°. It may be significant that on a flattened model with N and C intervalency angles of 120° and 110°, respectively, the R–N and H–C directions intersect at 65°, while for a regular 5-ring (such as XIX, XX, etc.) the corresponding angle should be 72°. These calculations, although too sensitively affected by variations in the component values adopted to justify more than semi-quantitative conclusions, nevertheless indicate nothing *against* the idea that sydnones contain a common structural atomic arrangement. The case of quinoline (*J.*, 1935, 1470) may be cited as an extreme analogy since its moment can appear to act over a range of 50° in various alkylquinolines or over a range of 33° in the 5-, 6-, and 8-nitro-derivatives; yet the quinoline nucleus indubitably persists throughout.

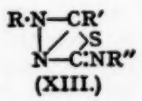
The next point for remark is the general high order of moment now found for sydnones. Uncertainties of space formulation and absence of analogies make it difficult to forecast a series of " expected " values for the two unperturbed " Lewis " structures (VI) and (X) which have been included in earlier discussions (Earl and Mackney, *loc. cit.*; Earl, *Nature*, 1946, **158**, 909). For (X) we have already noted (*Nature, loc. cit.*) that the moments of *N*-nitroso-methyl- and -ethyl-anilines are 3·62 and 3·61 D., respectively (Cowley and Partington, *J.*, 1933, 1252), while that of keten is 1·45 D. (Hannay and Smyth, *J. Amer. Chem. Soc.*, 1946, **68**, 1357), so that the highest likely moment of a molecule containing these units without modification is 5·1 D. Regarding (VI), Sutton *et al.* (*loc. cit.*) comment that its moment should not be greater than that of a γ-lactone (4·12 D.; Marsden and Sutton, *J.*, 1936, 1383). The measured figure is, however, *ca.* 2·4 D. more.

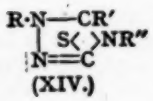
In our preliminary note (*Nature, loc. cit.*) we interpreted the results then available as indicating mesomerism (Ingold, *Chem. Reviews*, 1934, **15**, No. 2; Sutton, *Trans. Faraday Soc.*, 1934, **30**, 789; Zahn, *ibid.*, p. 804) between a number of dipolar extreme forms. Many of the stereochemically awkward " bridged " formulations proposed by earlier workers are now rewritten in this way. The various " endo "-compounds discovered by Busch and his collaborators (*J. pr. Chem.*, 1899, **60**, 187; 1903, **67**, 201, 216, 243, 257, 263; 1930, **124**, 301; *Ber.*, 1905, **38**, 4049) include some relevant examples, such as the " isodithiobiazolones " (XI) or (XII), the " thiotriazolines " (XIII) or (XIV), " nitron " (XV) or (XVI), etc. Schönberg (*J.*, 1938, 824), referring to the conceptions of Ingold (*J.*, 1933, 1120) and Sidgwick (*J.*, 1937, 694), suggested that the real states of Busch's compounds are resonance hybrids to which betaine forms such as (XVII) or (XVIII) contribute.

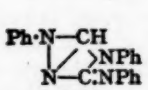

(X.)

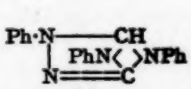

(XI.)

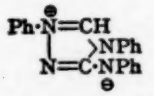

(XII.)

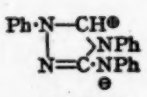

(XIII.)


(XIV.)


(XV.)

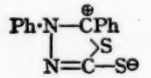

(XVI.)


(XVII.)

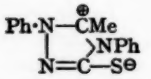

(XVIII.)

As mentioned on p. 2272, a fully formed zwitterion should have a moment of 20 or more D. units. Ingold's and Sidgwick's treatment, on the other hand, allows a lower moment than this to be observed experimentally; in fact, nitron shows $\mu = 7{\cdot}2$ D. (in benzene; Warren, *J.*, 1938, 1100). In the same way the unexpectedly high moments of a number of α- and

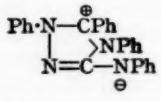
γ-pyrones (for some of which, incidentally, " bridged " structures were once current; see Collie, *J.*, 1904, **85**, 971; Homfray, *J.*, 1905, **87**, 1443) have been ascribed to contributions from several forms, certain being completely polar (Hunter and Partington, *J.*, 1933, 87; Le Fèvre and Le Fèvre, *J.*, 1937, 196, 1088). Jensen and Friediger (*Kgl. Danske Vidensk. Selsk.*, 1943, **20**, No. 20) have recently made a valuable and comprehensive dipole-moment study of resonance effects among heterocyclic systems, including nine of Busch's compounds, eight of which show high polarity, exemplified by the following :



" 2 : 3-Diphenyl-2 : 5-endothio-1 : 3 : 4-thiodiazolin," $\mu = 8{\cdot}8$ D. in C_6H_6 or 9·1 D. in dioxan.



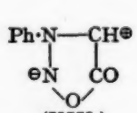
" 1 : 4-Diphenyl-5-methyl-3 : 5-endothio-1 : 2 : 4-triazolin," $\mu = 8{\cdot}4$ D. in $CHCl_3$.



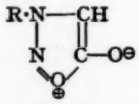
" 1 : 4 : 5-Triphenyl-3 : 5-endoanilo-1 : 2 : 4-triazoline," $\mu = 9{\cdot}1$ D. in C_6H_6 or 8·8 D. in dioxan.

These authors also explain their results by mesomerism between polar " amphoionen ", but mention as probable " das für die Konstitution dieser Verbindungen auch unpolare, biradikaloide Formeln von Bedeutung sind ".

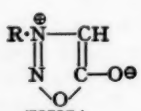
Arising out of the considerations noted above, we therefore imagine each sydnone to be a stable hybrid, containing a roughly regular 5-ring, to which (VI), (X), and several dipolar structures [*e.g.*, (XIX)—(XXII)] may contribute. Formula (XIX) is the activated form of



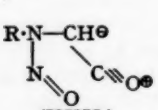
(XIX.)



(XX.)



(XXI.)

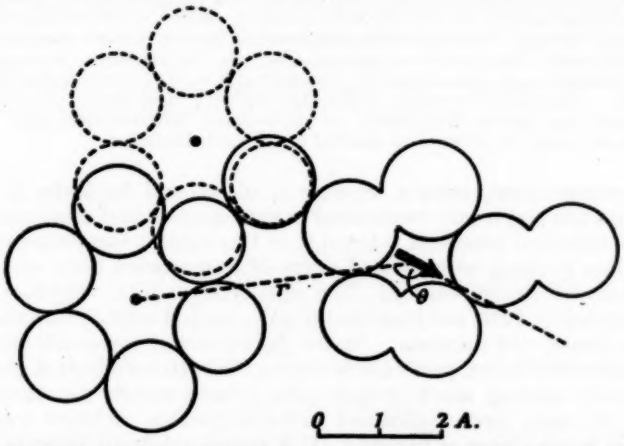


(XXII.)

(VI) [without the charge signs (XIX) would correspond to the " biradikaloide " formulæ of Jensen and Friediger, *loc. cit.*]; (XX) has some analogies with the polarised α-pyrones (cf. Clayton, *J.*, 1908, **93**, 524) and, further, the nitroso-group is known to act as a " donor ", forming 5- or 6-rings, in the metallic derivatives of " cupferron " or the nitroso-naphthols; (XXII) is suggested because a 25% contribution of $\overset{\ominus}{C}H_2—C\equiv\overset{\oplus}{O}$ has to be assumed to explain the observed dipole moment of keten (Hannay and Smyth, *loc. cit.*) *vis à vis* that of an ordinary ketone. Neither (X) nor (XXII) can be eliminated on the ground that sydnones do not react chemically as nitroso-compounds, since some of the metal complexes just cited also fail in this respect; (XXI) corresponds to the formula given by Kenner and Mackay (*Nature*, *loc. cit.*) to the monobromination product of *N*-phenylsydnone. The directions of action of the high moments expected for each of the contributors will clearly differ sufficiently for their effects, in the real state, to be diminished by partial mutual cancellation. They are not undetectable, however, and from the conclusion drawn earlier (p. 2273) it is evident that forms with the substituted nitrogen bearing a positive charge (such as XXI) predominate.

We have previously mentioned the possibility that mesomeric shifts may also occur in the aryl radicals of sydnones, thus allowing quadripolar forms further to affect the observable moments. The low value (Table III) for *N*-benzylsydnone (where conjugation with N is broken by interpolation of $>CH_2$) and the high moment of *N*-naphthylsydnone *could* partly be caused in this way. We now note, however, that electrostatically induced moments in the various nitrogen-held groups would qualitatively appear to operate in the same sense. Any substituent on the nitrogen atom will be more or less in line behind the point of action of the principal moment and hence (cf. Smallwood and Herzfeld, *J. Amer. Chem. Soc.*, 1930, **52**, 1919) the induced and principal moments will augment one another. With the benzyl derivative, the phenyl ring will obviously be some 70° (*i.e.*, 180° − 110°) out of line. Calculations on this suggestion must be somewhat uncertain since neither the *precise* position nor the value of the " nucleus " moment is known. Generally, however, the moments, μ_x and μ_y, induced in a group whose polarisability is equivalent to α c.c. at $(r)(\theta°)$, by a primary dipole, μ, situated at the pole and acting along the original line of a set of plane polar co-ordinates, are given by $\mu_x = \alpha\mu[(\varepsilon + 2)/3\varepsilon][(3\cos^2\theta - 1)/r^3]$ and $\mu_y = \alpha\mu[(\varepsilon + 2)/3\varepsilon][(3\sin\theta\cos\theta)/r^3]$, ε being the di-

electric constant of the intervening space ($\doteqdot 2{\cdot}4$), so that when the vectorial angle θ is *between* 55° and 125° μ_x and μ will not co-operate but oppose.



Drawn using the following interatomic distances (A.): C–C, 1·54; CAr.–CAr., 1·46; N–N, 1·48; O–O, 1·48; C–O, 1·43; C–N, 1·47; C=O, 1·28, and N=O, 1·18 (*Pauling and Huggins*, Z. Krist., 1934, **87**, 205; *Schomaker and Stevenson*, J. Amer. Chem. Soc., 1941, **63**, 37).

If the " nucleus " moment (see p. 2273) is located as indicated in the figure, and the C_6H_5 polarisability is effectively at the centre of the Ar-ring, the scale drawing shows that θ in benzylsydnone is between 140° and 150° while that in phenylsydnone (broken lines) is approximately 180°. The radius vectors, r, are likewise *ca.* 4·6 and 4·0 A., respectively. In the two molecules μ_x should therefore augment μ in each case, but in the ratio 1 : 3. On the basis of the figure and Stuart and Volkmann's estimate ($1{\cdot}23 \times 10^{-23}$ c.c.; *Ann. Physik*, 1933, **18**, 121) of α for the plane of the benzene ring, μ_x for *N*-phenylsydnone appears to have an absolute value of $0{\cdot}235\mu$ unit (whence, from our measurements, μ is around 5·3 D.), while for the benzyl compound $\mu_x = 0{\cdot}42$ and $\mu_y = 0{\cdot}57$ D., so that the resultant induced moment is 0·7 D. acting in the general direction of the principal moment. Although the application of more refined calculations, *e.g.*, the method of Sugden and Groves (*J.*, 1937, 1992), would probably produce somewhat lower figures, nevertheless it is evident that induction effects *alone* may easily account for the relative moments observed for benzyl- and phenyl-sydnones.

By similar arguments, the resultants for *N*-β-naphthyl-, *N-cyclo*hexyl-, and *N*-phenylsydnones should diminish in the order named, *i.e.*, the order of the polarisabilities of naphthalene, *cyclo*hexane, and benzene for which $[R_L]_D = 44{\cdot}4$, 27·7, 26·1 c.c., respectively. This is the order found by experiment.

The authors are grateful to Mr. J. Delmenico for the preparation of various specimens including the hitherto undescribed benzyl ester of *N*-nitrosophenylglycine (selected since it is solid at ordinary temperatures), and to the Chemical Society for permission to retain certain apparatus previously purchased with grants from their Research Fund.

UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, February 18th*, 1948.]

---

461. *The Autoxidation of Methyl Oleate and Linoleate, and the Decomposition of the Oxidation Products: A Theoretical Discussion.*

By G. PHILIP GIBSON.

By the logical development of a free-radical hypothesis an attempt is made to explain the results obtained when methyl esters of the C_{18} acids from palm oil are partly oxidised and then distilled. The activation of the molecules is considered to proceed by bond fission, each broken bond resulting in *two* centres of activity which may rearrange to form free radicals or new bonds. Components that may be activated are an oxygen molecule, and methylene, tertiary carbon, or unsaturated groups. The autoxidation is divided into two stages: (i) the induction period, during which the initial formation of a hydroperoxide from methyl linoleate takes place,

and (ii) the autoxidation proper, which is catalysed by the hydroperoxide. Stage (ii) is a chain-reaction cycle operating through the H— and HOO— free radicals. The structure of the hydroperoxides from methyl oleate and linoleate is forecast.

The hydroperoxides decompose more or less quickly and reaction occurs through either (A) an oxygen atom diradical, —O—, or (B) a hydroxyl radical, —OH. A hydroperoxyl group attacks methylene, tertiary carbon, or unsaturated groups within its own or other molecules, which may, thereby, be split into two parts or give mono-, di-, or tri-meric products. The chief decomposition products are considered to be derivatives of α-unsaturated hydroxy-esters, ·CH:CH·CH(OH)·, αβ-dihydroxy-esters, ·CH(OH)·CH(OH)·, and carbonyl compounds, ·CO·. Figures and tables are given illustrating the activation, autoxidation, and decomposition reactions which are likely to occur with methyl oleate and linoleate.

THE unsaturated system, comprising a mixture of oleate and linoleate, is of very frequent occurrence in oils and fats and it may be exposed to autoxidation and subsequent heat treatment in many natural or technical processes. Interest in this subject was stimulated by anomalous results obtained when working with methyl esters of unsaturated fatty acids which normally can be distilled without decomposition. The phenomenon was, therefore, investigated by deliberately autoxidising (p. 2290) and then distilling C_{18} methyl esters from palm oil which consist of methyl stearate, oleate, and linoleate. In the distillation of these autoxidised esters a high vacuum was not easily maintained, particularly during the initial and final stages of the operation. During the preliminary heating, the hydroperoxides present rapidly decomposed, the peroxide value quickly fell to zero, and unpleasant non-condensable vapours were evolved. The distillation products, briefly, were as follows: (1) A yellow aldehydic fraction, which amounted to 30—40% by weight of the initial hydroperoxide and was more volatile than the C_{18} methyl esters. (2) Colourless unoxidised esters. (3) A yellow oil less volatile than the C_{18} methyl esters. (4) A brown residue which was the main oxidation product and weighed twice as much as the hydroperoxide consumed; its iodine value, 63—65, showed to what extent the unsaturation had been reduced by oxidation, and it had a higher saponification value than that of the original ester in spite of the addition of oxygen to the molecule.

During autoxidation, hydroperoxidation was accompanied by loss of iodine value. This is in agreement with the work of Hilditch and Atherton (*J.*, 1944, 105) and Paquot (*Oleagineux*, 1947, 15). Farmer and Sutton (*J.*, 1943, 119) and Bolland (*Proc. Roy. Soc.*, 1946, *A*, 186, 218), however, maintain that hydroperoxidation proceeds without loss of unsaturation.

When saponified, autoxidised esters darkened appreciably; those that had been heated above 100° darkened more than those that had not.

In this paper an explanation is presented for the mechanism of autoxidation in the case of methyl oleate and linoleate, and for the simultaneous or subsequent thermal decomposition of the autoxidised products. The explanation follows from a consideration of experimental data both of the author and of many other workers. The basis of the hypothesis is the activation of covalent bonds before their breaking, and the sharing, between the affected atoms, of the liberated free energy which accompanies the activation. Thus when a bond is activated and is about to break, *two* centres or regions of activity are formed, one at each of the atoms to which the bond was attached. It appears probable that an active centre is in fact due to a particular state of excitation of one of the electrons which formed the original bond. Throughout this paper centres of activity are shown diagrammatically in short heavy lines.

Three cases have to be considered, as shown under activation of covalent bonds in Fig. 1. First, by breaking of a single bond, two free radicals are formed with a centre of activity in each of two separate molecules or atoms. Secondly, by rupture of one of the bonds in a double bond only a diradical can be formed with two centres of activity in one molecule. Finally, by breaking of the two bonds of a double bond simultaneously, two free diradicals are formed with centres of activity in each of two separate molecules or atoms. Centres of activity may be formed only momentarily and may react further according to the experimental conditions to form free radicals or new bonds as follows:

(I) The atoms or groups of atoms to which the centres of activity are attached may assume a separate existence as free radicals (Reaction I, Fig. 1).

(II) A free radical formed by Reaction I may attack an activated or breaking bond and give a new bond and a new free radical (Reaction II, Fig. 1). This mechanism is typical of a chain reaction and is the means whereby activity is transferred from atom to atom. Such reactions involving free radicals usually occur at a high speed.

(III) Two activated bonds may react together to form new bonds (Reaction III, Fig. 1). Reactions of this type take place at a low speed.

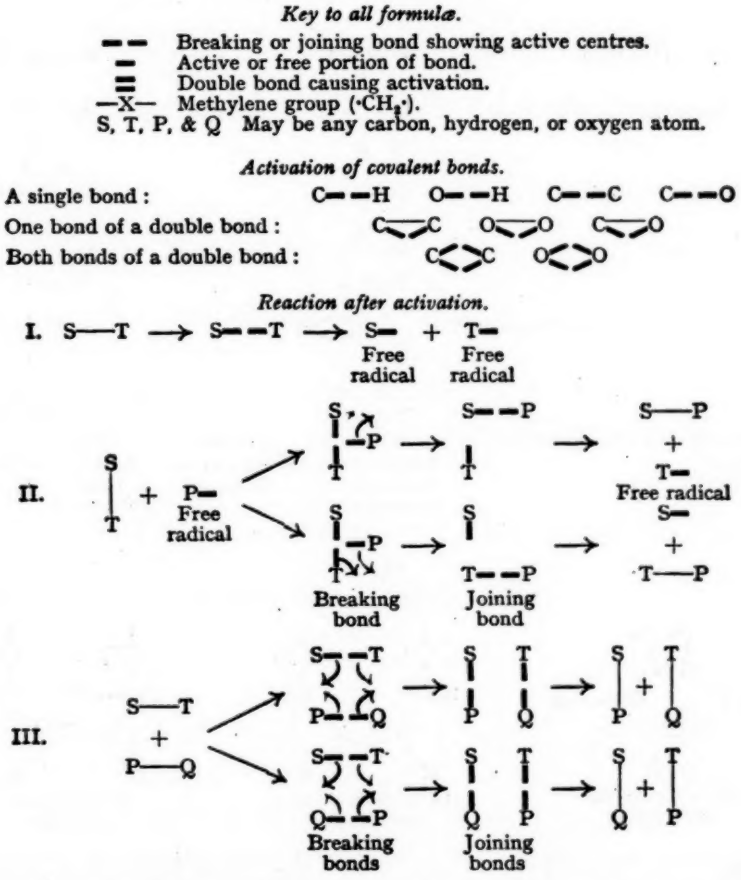
The extent of the activation is extremely small, possibly of the order 10^{-12} mole; it is to be

regarded rather as a tendency for a bond to break than as an equilibrium between two free radicals.

Components that may be activated are oxygen molecules, methylene groups, tertiary carbon groups, and unsaturated groups. The oxygen molecule will be considered first, and then that of the unsaturated system. The latter includes the general case of an isolated double bond as in methyl oleate, that of two double bonds separated by a methylene group as in methyl linoleate, and finally that of two conjugated double bonds. The last-named system, although not at first present, occurs in autoxidised methyl linoleate.

FIG. 1.

General scheme for activation of organic molecules, for formation of free radicals, and for reaction between active bonds.



The oxygen molecule may be activated as shown in Fig. 2. It is the simplest component of an autoxidising system and always gives rise to an active diradical. By Reaction II, Fig. 1, the oxygen molecule and an active hydrogen atom produce an active hydroperoxyl radical. These radicals, and others containing oxygen, may react in either the bivalent or the quadrivalent state.

In the case of an isolated double bond, the activation of the molecule is shown in Fig. 3 and Fig. 4 (*a*). α-Methylene groups, usually present on either side of the unsaturated group, may become activated by the double bond [Fig. 3 (1)]. Besides the ordinary additive properties of the double bond which may be represented by Fig. 3 (2), there is also the possibility of combined activity as in Fig. 3 (3). In this, the two activities, Fig. 3 (1) and (2), are stimulated at the same time, the free energy being suitably distributed over four atoms. Combined activity, Fig. 3 (3), occurs during the rotations of the activated parts of the bonds when they are spatially

near each other. Such a situation arises frequently where there is free rotation of the methylene group about the C–C axis as in oleic acid, but not at all when the groups are locked in a ring as

FIG. 2.

Alternative states for oxygen, hydroperoxides, and related molecules.

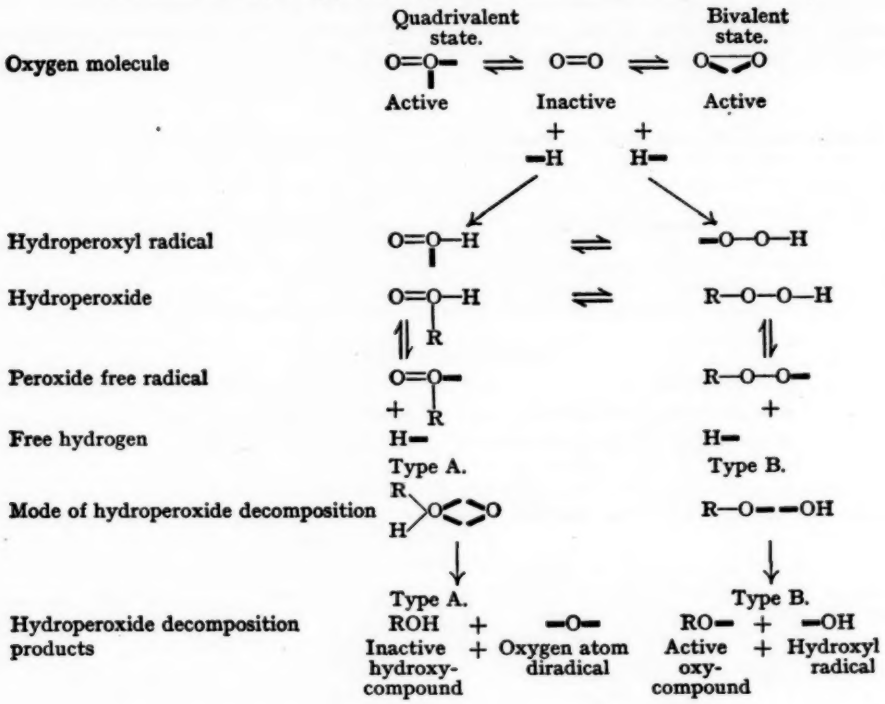
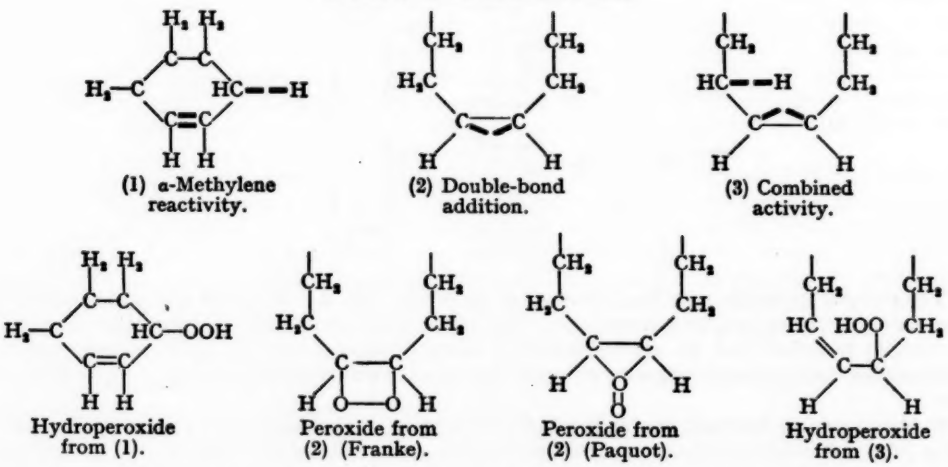


FIG. 3.

Modes of attack on double bonds.



in *cyclo*hexene. The mechanism of autoxidising fatty unsaturated molecules is best explained by this combined activity [Fig. 3 (3)].

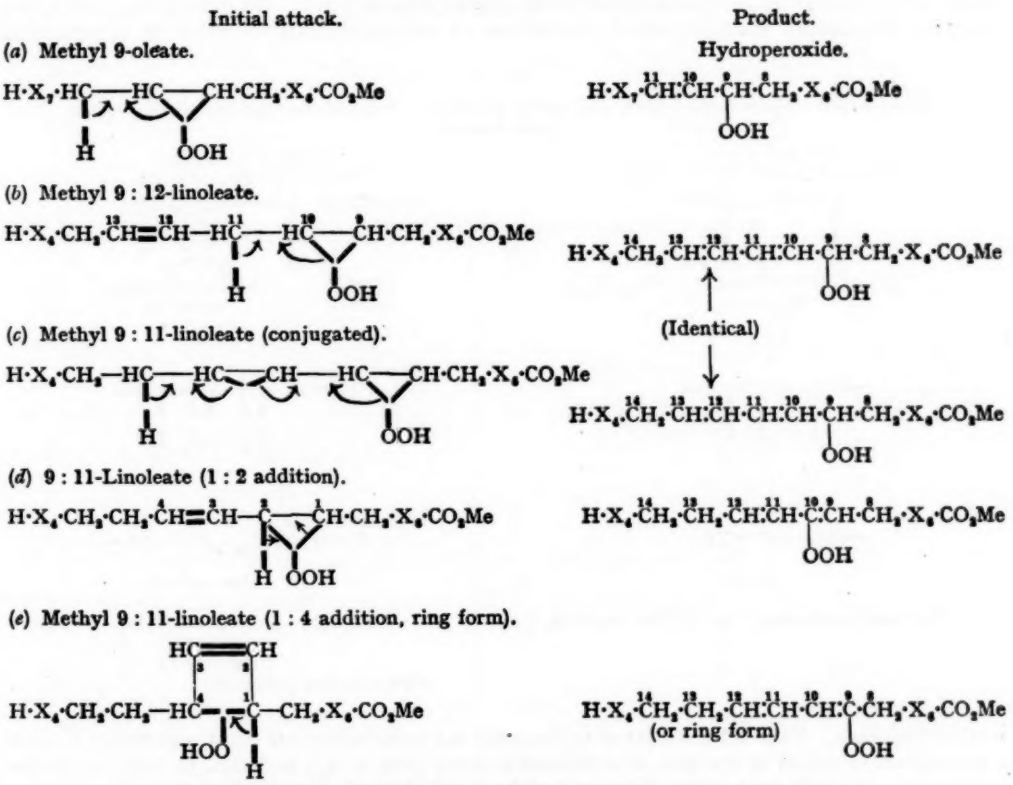
The activity associated with the linoleate system is of a much higher order than that of an isolated double bond. Unsaturated groups on either side of the 11-methylene group are

responsible for this enhanced effect. The activation of the linoleate molecule before autoxidation is shown in Fig. 4 (*b*).

For the activation of the conjugated linoleic system, free energy may be transferred along the chain of unsaturation so that a relatively distant α-methylene group becomes activated for hydrogen abstraction, as shown in Fig. 4 (*c*). The examples, Fig. 4 (*a*), (*b*), and (*c*), of activity in the system methyl oleate–methyl linoleate are cases of the combined activity previously discussed [Fig. 3 (3)]. In the conjugated linoleate, there is a further possibility. The resonating bonds present therein so reinforce or react with each other that α-methylene activity comes into play [Fig. 3 (1)] as in *cyclo*hexene or tetralin. Thus, any of the four tertiary carbon atoms in the conjugated system may become activated because of their α-relationships

FIG. 4.

Types of hydroperoxides formed from methyl oleate and linoleate below 60°.


Initial attack.
Product.
(a) Methyl 9-oleate.
Hydroperoxide.
(b) Methyl 9 : 12-linoleate.
(c) Methyl 9 : 11-linoleate (conjugated).
(Identical)
(d) 9 : 11-Linoleate (1 : 2 addition).
(e) Methyl 9 : 11-linoleate (1 : 4 addition, ring form).
(or ring form)

[Type of activity (cf. Fig. 3) is: (*a*)—(*c*), type (3); (*d*)—(*e*), type (1)].

to double bonds. The tertiary-carbon activation of the ordinary form of conjugated linoleate is shown in Fig. 4 (*d*), and that of the extreme 4-ring form in Fig. 4 (*e*). As autoxidation progresses, the types of activity shown in Fig. 4 (*c*), (*d*), and (*e*) develop and play an increasing part in the reaction, although they are not present originally.

The activation of molecules shown in Figs. 1—4 is concerned primarily with autoxidation, but it is evident that the principle is of very general application. The decomposition of hydroperoxides has been interpreted on this basis. The hypothesis could readily be applied to other processes requiring hydrogen abstraction such as condensation, or to those catalysed by light or heat such as polymerisation. Spatial proximity of reacting groups is an important factor in this connection; *e.g.*, reaction between the 1- and the 4-position may occur in suitable circumstances.

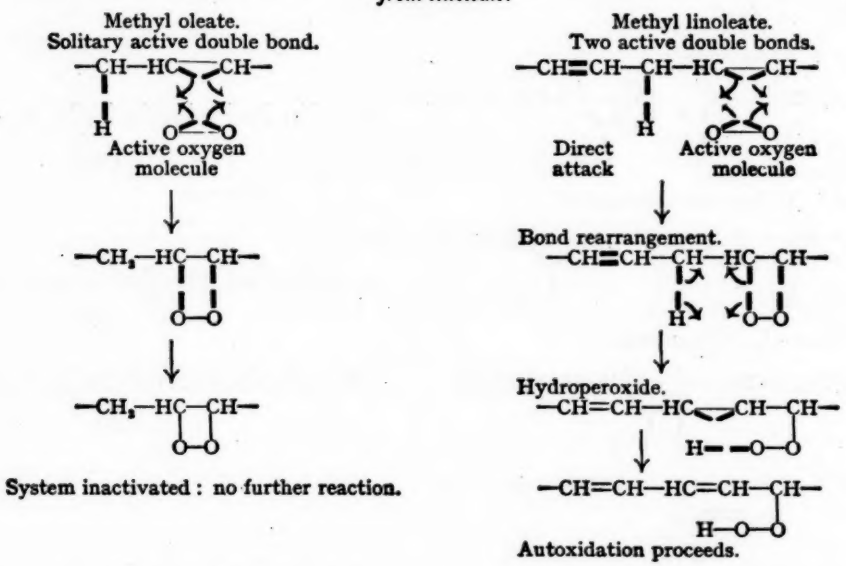
During recent years, many investigations have been carried out on the autoxidation of unsaturated esters, and with reference to Fig. 3, (1), (2), and (3), emphasis has been laid on: (1) attack at the methylene groups adjacent to the double bond assisted by the presence of

active or free atoms and radicals (Farmer, Bloomfield, Sundralingam, and Sutton, *Trans. Faraday Soc.*, 1942, **38**, 348) [Fig. 3 (1)]; (2) direct attack at the double bond (Hilditch and Gunstone, *J.*, 1945, 836; 1946, 1022).

It appears that in (1) hydrogen is removed from an α-methylene group and is replaced by a hydroperoxyl group. The double bond remains in position to yield in the case of oleate the 9-unsaturated 8- or 11-hydroperoxide. On the addition of oxygen to the double bond as suggested by Franke and Paquot [see Fig. 3 (2)], however, there is no hydrogen abstraction and the double bond is completely saturated. As there is no direct experimental evidence to support these hypotheses, Farmer has introduced the idea of mesomerism in an endeavour to harmonise the facts with his α-methylene theory [Fig. 3 (1)]. Such reactions, however, do not occur till 180° is reached and would involve the conjugative isomerisation of a large part of the linoleate which has not been observed. According to Hilditch [see (2) above], the primary addition of oxygen to the double bond is followed by an indefinite rearrangement of the bonds, including those of the methylene groups adjacent to the original double bond. On these grounds Hilditch explains the almost stoicheiometric production of conjugated unsaturation in autoxidising

FIG. 5.

Comparison between methyl oleate and methyl linoleate : Initial formation of hydroperoxides from linoleate.



methyl linoleate. This led the author to consider the possibilities for bond movement in such a system and resulted in the idea of combined activity [Fig. 3 (3)], and this, in turn, led to the postulation of a satisfactory mechanism for the autoxidation of methyl oleate and linoleate.

The mixture of oleate and linoleate has already been considered by Hilditch and Gunstone (*loc. cit.*). They showed that methyl oleate free from linoleate is very resistant to autoxidation but that the reaction may be catalysed by methyl linoleate. A hydroperoxide also acts as a catalyst (Bolland, *loc. cit.*). Light or heat accelerates autoxidation and the induction period can then be reduced to vanishing point. During the autoxidation of methyl linoleate itself there is no appreciable induction period (Bolland, *locc. cit.*; Bergstrom, *Arkiv Kemi, Min., Geol.*, 1946, **21**, *A*, 1), and a hydroperoxide is obtained directly on treatment with oxygen. The reaction mechanism for methyl linoleate, therefore, differs from that for methyl oleate.

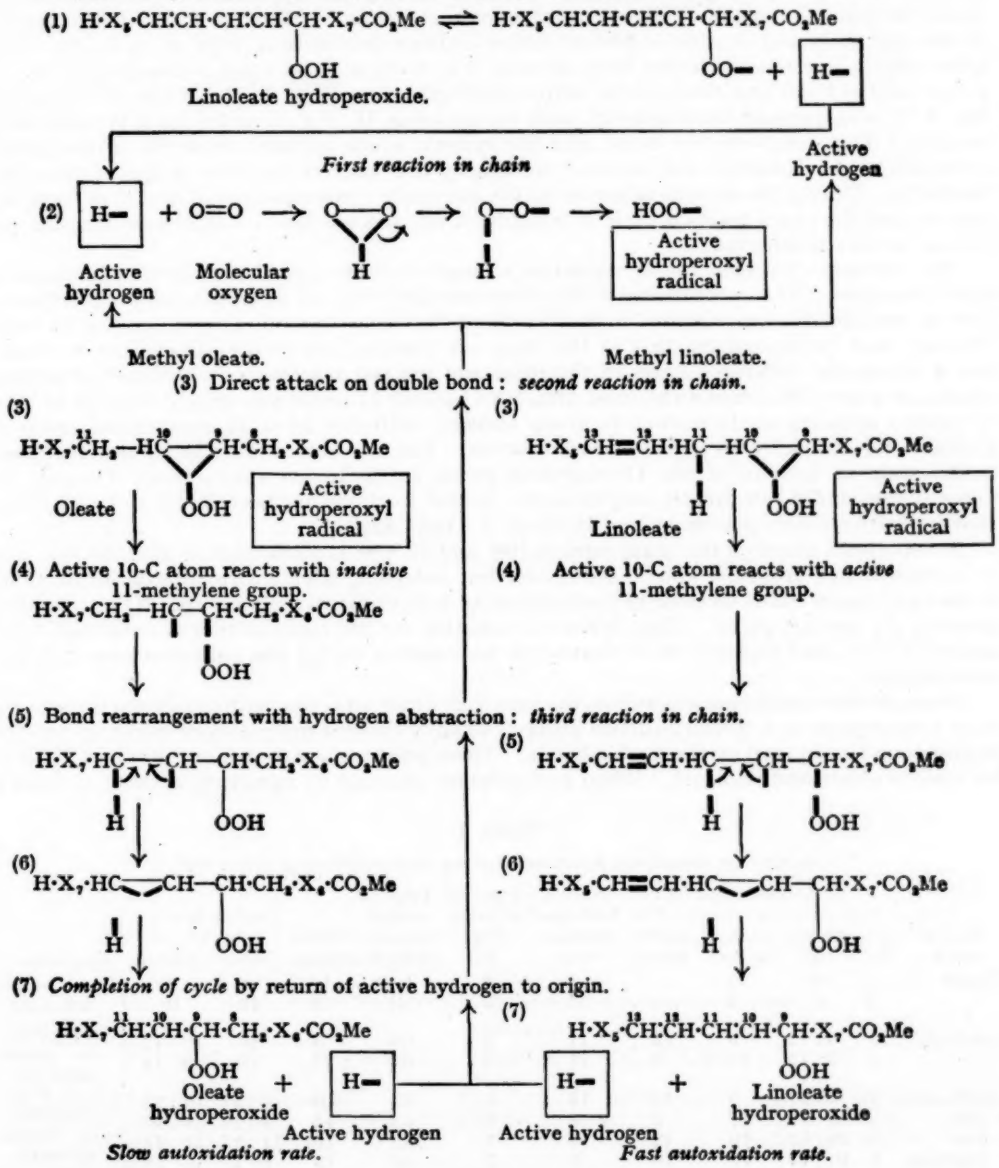
The autoxidation of a mixture of methyl oleate and linoleate, however, has a well-defined induction period and the reaction is typically auto-catalytic. It may be divided into two stages : (i) the induction period, when the initial formation of a hydroperoxide from methyl linoleate and oxygen is taking place, and (ii) the autoxidation proper, in which both methyl oleate and linoleate are undergoing oxidation catalysed by the hydroperoxide formed in (i).

In order to account for the slow initial reaction (i), it is suggested that molecular oxygen when activated by light or heat contains a small concentration of an active diradical in which

there are two points of activity as shown in Fig. 2. This active oxygen molecule attacks the linoleic molecule, which is activated as shown in Fig. 3 (3), by Reaction III, Fig. 1. After this initial attack, a second double bond is still present having its full capacity for activating the α-methylene group. One of the hydrogen atoms of this group is, therefore, transferred to one

FIG. 6.

Propagation of the chain reaction for forming hydroperoxides from methyl oleate and linoleate.



of the oxygen atoms again by Reaction III, Fig. 1, and a hydroperoxide is formed as illustrated in Fig. 5. The high activity in the linoleic system contrasts strongly with the very low activity in the oleic system (Fig. 5). When a double bond, as in methyl oleate, is attacked, the adjacent methylene groups lose their activity because the source of this activity—the double bond—has been saturated. The two molecules mutually deactivate each other and there is no further reaction.

Once a critical but small concentration of hydroperoxide is reached through reaction (i), corresponding in the present case to a Lea figure of 20, the system becomes autocatalytic (ii) and oxidation then proceeds at a high but steady rate. A mechanism depending on a chain-reaction cycle is required to account for this behaviour. It is evident that a hydroperoxide in the presence of oxygen can supply the active radicals necessary for the propagation of such a chain reaction. It is suggested, as shown in Fig. 6, that these active chain carriers are the free hydrogen and hydroperoxyl radicals (—H and —OOH, respectively). A hydroperoxide formed during the induction period (i) gives an active hydrogen atom by Reaction I, Fig. 1, which then reacts with molecular oxygen to give an active hydroperoxyl radical [Figs. 2 and 6 (2)]. The latter attacks any nearby double bond directly [Fig. 6 (3)] and, by bond rearrangement, forms a new double bond and liberates an active hydrogen atom [Fig. 6 (5)]. These three stages, Fig. 6 (2)—(6), proceed consecutively, each by Reaction II, Fig. 1, and form a typical chain reaction. This completes the cycle, and the system, which initially gives rise to the active hydrogen, is not disturbed and does not necessarily take part in the other stages of the autoxidation. During the induction period (i) the necessary concentrations of active radicals for propagating the chain-reaction cycle is being built up, and reaction becomes autocatalytic (ii) as soon as this is achieved.

The difference between the autoxidation of methyl oleate and that of methyl linoleate is again emphasised when considering it as a chain-reaction cycle (cf. the induction period above). This is very clearly demonstrated in Fig. 6, where the chain reactions are set out side by side. The first and the second reaction in the chain are identical for methyl oleate and linoleate, but a substantial difference arises in the third and the last reaction. In the case of methyl oleate, an active 10-carbon atom must attack an *inactive* 11-methylene group, whereas in that of methyl linoleate an 11-methylene group strongly activated by a 12-unsaturated group is available for attack by an active 10-carbon atom. The rate-determining factor in either case is the state of activity of the 11-methylene group for hydrogen abstraction. The rate of autoxidation under comparable conditions for methyl linoleate has been found to be 12 times that for methyl oleate (Gunstone and Hilditch, *J.*, 1945, 836).

A hypothesis based on the chain carriers H— and HOO— is considered by Bolland (*loc. cit.*) to be satisfactory from the kinetic standpoint but untenable from a structural point of view. A chemical theory based on these radicals and on an active oxygen molecule O⟨⟩O is, however, given in the present paper. This, besides accounting for the autoxidation as catalysed by a hydroperoxide, also explains the formation of the catalyst during the induction period of the autoxidation.

The activity of hydrogen atoms, *i.e.*, the ease with which an active hydrogen atom is removed from a methylene or a tertiary carbon group, probably decides the positions taken up by the hydroperoxyl group and by the double bonds. These positions are shown in Fig. 4 and Table I for methyl oleate and linoleate. When autoxidation proceeds by combined activity as shown

TABLE I.

Changes in structural positions during autoxidation at below 60°.

Methyl ester.	No.	Double bond(s): Original.	Attacked.	Activating.	Active hydrogen abstraction.	Type of activity (Fig. 3).	Type of initial attack (Fig. 4).	·OOH group.	Double bonds: New.	Total.	Remarks.
Oleate	1	9	9	—	8	3	(a)	10	8	8	In equal amounts
	2	9	9	—	11	3	(a)	9	10	10	
Linoleate	1	9 : 12	9	12	11	3	(b)	9	10	10 : 12	Conjugated in equal amounts
	2	9 : 12	12	9	11	3	(b)	13	11	9 : 11	
Linoleate after conjugation	1	9 : 11	9	11	13	3	(c)	9	10 : 12	10 : 12	Conjugated in equal amounts
	2	9 : 11	11	9	8	3	(c)	12	8 : 10	8 : 10	
	3	10 : 12	10	12	14	3	(c)	10	11 : 13	11 : 13	
	4	10 : 12	12	10	9	3	(c)	13	9 : 11	9 : 11	
1 : 2-Addition	5	9 : 11	9	11	10	1	(d)	10	9 : 11	9 : 11	Conjugated in equal amounts
	6	9 : 11	11	9	11	1	(d)	11	9 : 11	9 : 11	
	7	10 : 12	10	12	11	1	(d)	11	10 : 12	10 : 12	
	8	10 : 12	12	10	12	1	(d)	12	10 : 12	10 : 12	
1 : 4-Addition (ring form)	9	9 : 11	9 : 12	10	9	1	(e)	9	9 : 11	9 : 11	Conjugated in equal amounts
	10	9 : 11	9 : 12	10	12	1	(e)	12	9 : 11	9 : 11	
	11	10 : 12	10 : 13	11	10	1	(e)	10	10 : 12	10 : 12	
	12	10 : 12	10 : 13	11	13	1	(e	13	10 : 12	10 : 12	

in Fig. 3 (3), the primary attack occurs at the double bond and the hydroperoxyl group becomes attached at one of the double-bond carbon atoms. The double bond itself is displaced one

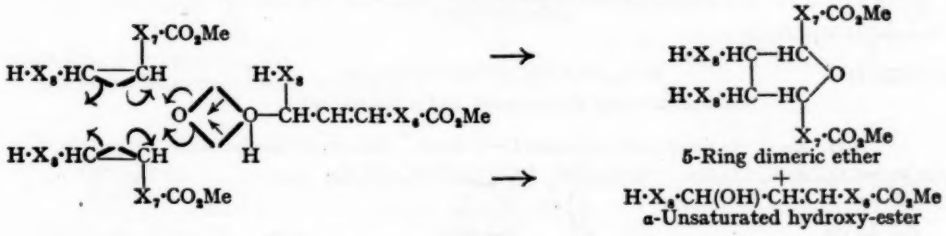
FIG. 7.

Initial ways of decomposing a hydroperoxide : Type A.

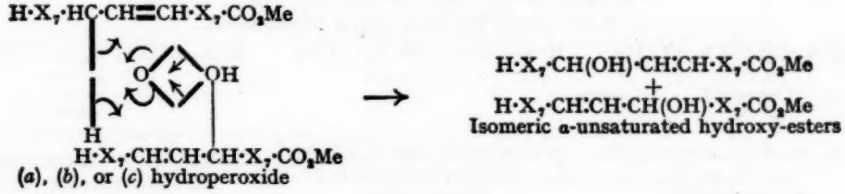
Type A : Reaction by addition of an —O— atom at 60°.

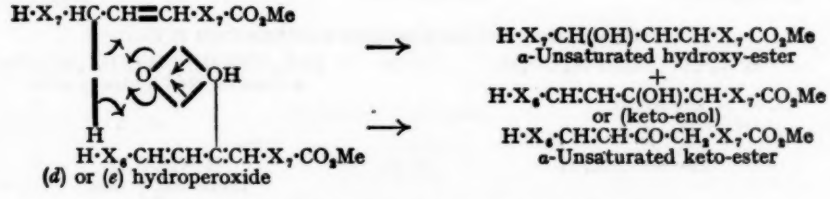
A I. An —O— atom with a double bond.

A II. An —O— atom with two double bonds.

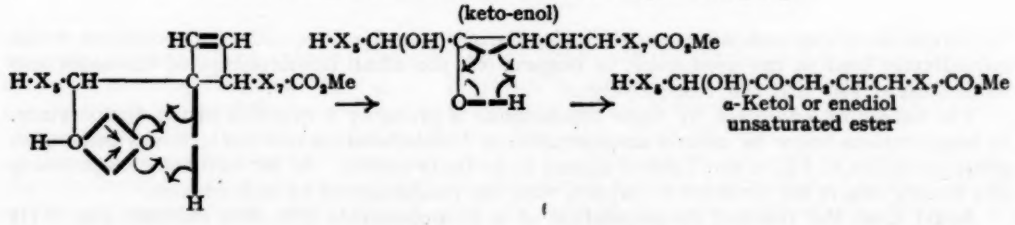


A III. An —O— atom with an active methylene group.





A IV. An —O— atom with an active tertiary carbon group.



place away from its original position, and hydrogen abstraction takes place from one of the α-methylene groups. Combined activity, Fig. 3 (3), thus produces methylene hydroperoxides as shown in Fig. 4 (*a*), (*b*), and (*c*). A modified form of α-methylene activity [Fig. 3 (1)]—

tertiary-carbon activity—on the other hand, gives by Reaction II, Fig. 1, tertiary-carbon hydroperoxides as shown in Fig. 4 (*d*) and (*e*).

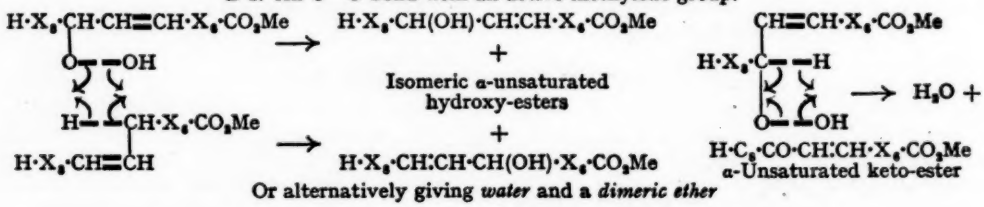
Methyl oleate gives isomeric α-unsaturated methylene hydroperoxides. Methyl linoleates *all* give *conjugated* diunsaturated hydroperoxides. The methylene hydroperoxides from 9 : 12- and from conjugated 9 : 11- or 10 : 12-linoleates are of identical type [Fig. 4 (*b*) and 4 (*c*)]. The tertiary-carbon hydroperoxides, however, are produced only from the conjugated linoleates and are of two types depending on whether the original linoleates react in the 1 : 2- or the 1 : 4-phase. The positions which may be occupied by double bonds and hydroperoxyl groups are somewhat restricted. In contrast, if the oleic and linoleic systems are first activated with

FIG. 8.

Initial ways of decomposing a hydroperoxide : Type B.

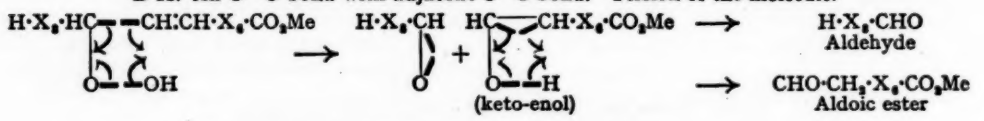
Type B : Reaction by fission of an O—O bond at 170°.

B I. An O—O bond with an active methylene group.

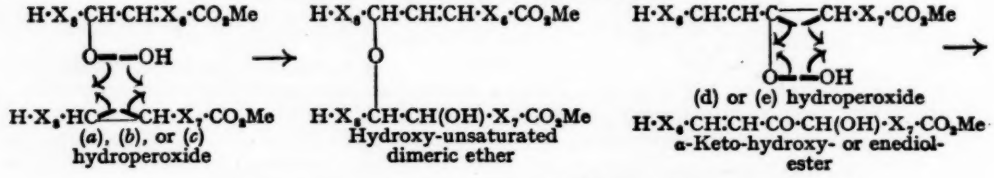


Or alternatively giving *water* and a *dimeric ether*

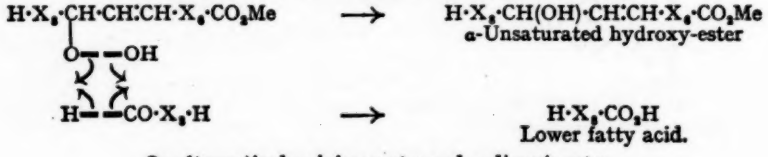
B II. An O—O bond with adjacent C—C bond. Fission of the molecule.



B III. An O—O bond with a double bond.



B IV. An O—O bond with an aldehyde from B II.



Or alternatively giving *water* and a *dimeric ester*.

the formation of free radicals as suggested by Farmer, mesomeric equilibrium conditions would immediately lead to the production of isomers (cf. the alkali isomerisation of linoleates and linolenates at 180° and 160, respectively).

The extent of activation by these mechanisms is probably a function of the temperature. At temperatures below 60° certain arrangements of double bonds in relation to the hydroperoxyl group as shown in Fig. 4 and Table I appear to be fairly stable. At 50° autoxidation proceeds at a steady rate in the presence of oxygen, with the production of hydroperoxides.

Apart from the thermal decomposition of a hydroperoxide into free radicals, Fig. 6 (1) (cf. Bolland, *loc. cit.*), hydroperoxides may also decompose by being themselves reduced in the ways indicated below. The reaction proceeds only slowly at 50° but rapidly at higher temperatures and may occur at even lower temperatures, particularly with esters containing more than one double bond (cf. Bergstrom and Holman, *Nature*, 1948, **161**, 55). Hilditch and

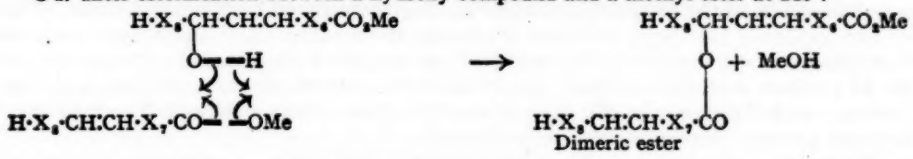
Gunstone (*loc. cit.*) have investigated autoxidations at temperatures up to 120°, and it is evident that formation and decomposition of hydroperoxide are proceeding simultaneously.

The initial decomposition of hydroperoxides (Fig. 2) can be accounted for in two ways, Type A and Type B. These reactions, as shown in Figs. 7 and 8 respectively, may take place additively at double bonds, with loss of iodine value [Fig. 3 (2)], or by hydrogen abstraction at active methylene or tertiary-carbon groups [Fig. 3 (1)], or by fission of an adjacent C–C bond. Decomposition reactions, Type A, occur at temperatures up to 60°. Hydroperoxides are assumed

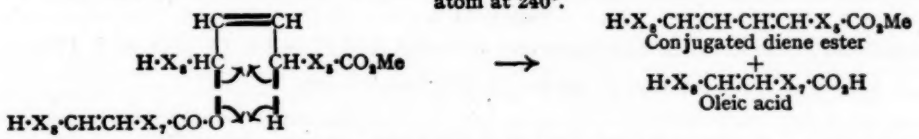
FIG. 9.

Secondary and miscellaneous reactions : Type C.

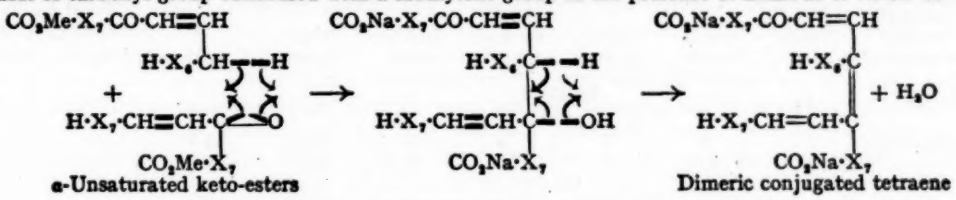
C I. Inter-esterification between a hydroxy-compound and a methyl ester at 240°.



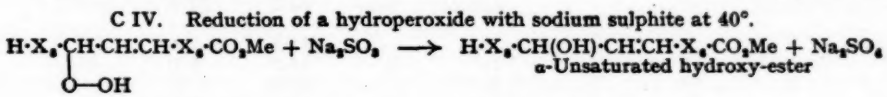
C II. Conjugated unsaturation by bond rearrangement in conjunction with an active hydrogen atom at 240°.



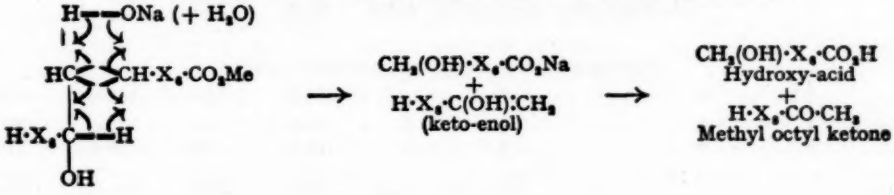
C III. A carbonyl group condensed with a methylene group in the presence of alkali at or below 80°.



C IV. Reduction of a hydroperoxide with sodium sulphite at 40°.



C V. Hydrolytic fission of an α-unsaturated alcohol with alkali at 190°.



to contain quadrivalent oxygen (Paquot, *loc. cit.*) and their decomposition proceeds through an —O— atom by Reaction III, Fig. 1. Type A (Fig. 7) resembles the oxidation of conjugated double bonds by perphthalic acid or perbenzoic acid, which proceeds in dilute solution at low temperatures (40°) (Karrer and Jucker, *Helv. Chim. Acta*, 1945, **28**, 427).

Type B occurs at temperatures above 100°, and decomposition proceeds normally through the rupture of an –O—O– group by Reaction III, Fig. 1, and the intermediate formation of an active hydroxyl radical; —OH, Fig. 2. At 170°, and in the absence of oxygen, this type of reaction (Fig. 8) is very rapid and all the hydroperoxide soon disappears.

At higher temperatures up to 240° the slow secondary reactions (Type C) shown in Fig. 9 take place during distillation by Reaction III, Fig. 1. A number of miscellaneous reactions are also included in Type C.

An attempt has been made to apply the above decomposition reactions to the hydroperoxides of methyl oleate and linoleate in the presence of an excess of methyl oleate without considering possible structural isomerism. The results of this extensive inquiry are summarised in the following discussion.

Recent work on the autoxidation of methyl oleate and linoleate shows that the initial products are respectively mixtures of α-unsaturated hydroperoxides and of αγ-di-unsaturated hydroperoxides, but the actual numerical location of these groups is not so certain. The separation of the mixed hydroperoxides is no easy matter, but concentration as far as 90% hydroperoxide in the case of methyl oleate has been achieved by molecular distillation (Farmer and Sutton, *loc. cit.*), and also by crystallisation at −80° (Swift, Dollear, and O'Connor, *Oil and Soap*, 1946, **23**, 255). Bergstrom (*loc. cit.*), in the case of methyl linoleate, has concentrated the autoxidation products by a process of fractional adsorption and desorption. Further structural delineation of the oxidised molecules has been attempted by these and other workers, but no clear evidence has been adduced regarding the structures of these hydroperoxides. Bergstrom has some evidence that, for methyl linoleate, the hydroperoxide groups are in the 9- or the 13-position and this evidence fits in with the present theory. On the other hand, Swift, Dollear, and O'Connor, in the case of methyl oleate, claim positions 8 and 11 for the hydroperoxide groups, contrary to the present theory.

TABLE II.

Aldehydic and acidic fission of hydroperoxides according to B II and B IV (Fig. 8) at 170°.

Hydroperoxide methyl ester.	No. (Table I).	Chain length.	Ester group.	Aldehyde or acid group.	Double bond.	Theoretical wt. (%) from hydroperoxides. Aldehyde.	Acid.	Total fission products (i) + (ii). Aldehyde.	Acid.
		position							
Fission products: (i) Dicarboxylic part.									
Oleate	1, 2	9	1	9	—	56·7	30·8	—	—
Linoleate	1	9	1	9	—	28·5	15·5	—	—
	2	12	1	12	9	34·7	18·6	—	—
				Linoleate, total		63·2	34·1		
Linoleate after conjugation	1	9	1	9	—	14·3	7·8	—	—
	2	11	1	11	8	16·3	8·7	(below)	
	3	10	1	10	—	15·3	8·3	—	—
	4	12	1	12	9	17·4	9·2	—	—
				Linoleate after conjugation, total		63·3	34·0		
Fission products: (ii) Monocarboxylic part.									
Oleate	1, 2	9	—	1	—	43·3	24·1	100·0	54·9
Linoleate	1	9	—	1	3	21·5	12·0	50·0	27·5
	2	6	—	1	—	15·3	8·9	50·0	27·5
				Linoleate, total		36·8	20·9	100·0	55·0
Linoleate after conjugation	1	9	—	1	3	10·7	6·0	25·0	13·8
	2	7	—	1	—	8·7	5·0	25·0	13·7
	3	8	—	1	3	9·7	5·5	25·0	13·8
	4	6	—	1	—	7·6	4·5	25·0	13·7
				Linoleate after conjugation, total		36·7	21·0	100·0	55·0

Since the decomposition products (Type B II *) more volatile than the original esters, and arising from fission of the molecule, indicate the positions initially occupied by the hydroperoxyl groups, a summary of the possibilities is given in Table II (cf. Swift, Dollear, Brown, and

* Type B II refers to Decomposition Reaction Type B II, Fig. 8.

O'Connor, *J. Amer. Oil Chem. Soc.*, 1948, **25**, 39). The molecule breaks into two parts at the site of a double bond before it is hydroperoxidised. One part of the broken molecule is an aldehyde and the other an aldoic ester. Methyl oleate thus gives C_9-aldehyde and 9-aldoic methyl ester. Methyl linoleate may divide at either the 9- or the 12-double bond; the second double bond then appears as a β-unsaturated aldehyde or acid. The fission products for conjugated methyl linoleate are of the same general nature but show more variation in chain length. The mode of formation of volatile unsaturated acids at an advanced stage in the autoxidation of methyl linoleate (Hilditch and Gunstone, *loc. cit.*) is thereby explained (Type B IV).

Similarly, the hydrolytic fission (Hargreaves and Owen, *J.*, 1947, 750, 753, 756), of the α-unsaturated hydroxy-compounds produced by the reduction of the hydroperoxides (Types A, B I, B IV, C V) may have some structural significance, for the oxygen of the hydroxyl group then appears in an acetyl group. The above scission products of roughly half the original molecular weight should be easy to separate and identify.

Farmer contends that there is no loss of unsaturation on autoxidation, as the absorption of oxygen is proportional to the degree of peroxidation; both Hilditch and Paquot, on the other hand, record a fall in iodine value roughly proportional to the extent of peroxidation. A fall of iodine value (4·5 units) is shown in Table III for 6·1% wt. peroxidation at 60° and a further fall (1·8 units) on distillation. The iodine value is not necessarily a correct index of the extent of unsaturation, for a discrepancy between them is well known with conjugated compounds. As these are almost absent in the present case at the beginning of an autoxidation, it would appear that the fall in iodine value represents a genuine loss of unsaturation. These apparently conflicting results, probably due to different experimental conditions, can, however, be reconciled on the assumption that hydroperoxidation occurs initially without loss of unsaturation, and that hydroperoxides decompose more or less slowly with loss of iodine value and of unsaturation (cf. Bergstrom and Holman, *loc. cit.*). Hilditch's data support this view very strongly, for towards the end of the absorption of oxygen, the extent of the hydroperoxidation, as shown by Lea figures, rises to a maximum and then falls equally sharply. There is apparently a change in the nature of the oxidation at about 70°; as this temperature is reached, the rate of decomposition of the hydroperoxide accelerates with increase of temperature, the rate being doubled for a 10° rise. The loss of iodine value has been frequently attributed to the formation of a stable peroxide of the cyclic ether type, particularly at high temperatures. Two possibilities, one due to Franke and Monch (*Annalen*, 1944, **556**, 1, 200) and the other due to Paquot (*loc. cit.*), involving quadrivalent oxygen, are illustrated in Fig. 3 (2). Both forms retain the peroxidic character and should still react with hydriodic acid, possibly at a slower rate, giving dihydroxystearic acid or a derivative thereof. The loss of unsaturation by the formation of dihydroxystearic compounds (Type A I, B III) may be balanced by the production of additional unsaturation, particularly at high temperatures, in the form of conjugated diene esters (Type C II; cf. pyrolysis of polyricinoleic acid to conjugated linoleic acid).

The most likely way in which the additive character of the double bond, with loss of unsaturation, is brought into play at low temperature is through Type A reactions (Fig. 7). Type B reactions (Fig. 8) are not, however, entirely ruled out. The mass-action effect of the presence of a large amount of methyl oleate should not be neglected.

Theoretically, the stable decomposition products may be placed in the following order of probability: (1) The most frequent product is an α-unsaturated hydroxy-compound (Types A, B I, B IV) or its ethers (Type B III) or esters (Types B IV, C I), which retains all the additive and α-methylene activities of a double bond. (2) Dihydroxystearate or its ethers (Type B III) including epoxy-groups (Types A I, B III), or esters (Types C I, C II) which, in contrast, are completely devoid of unsaturation but function entirely as αβ-dihydroxy-compounds. (3) Finally, a carbonyl group may be formed in which there is residual unsaturation between the carbon and oxygen atoms.

For any complete explanation of autoxidation, the oxygen distribution at the different stages in the process (*e.g.*, autoxidation, thermal decomposition, and saponification) is important in determining the course of reaction. Oxygen may be combined in any of the following ways: carboxyl (·CO_2Me, ·COO·, and ·CO_2H), hydroxy (·OH), epoxy and ether (·O·), carbonyl (·CO·), αβ-dihydroxyl [·CH(OH)·CH(OH)·] and enediol [·C(OH):C(OH)·].

No satisfactory explanation is available to account for the production of a dark brown colour on saponification of autoxidised products. It is unlikely that an α-unsaturated hydroxy-compound [see (1) above] or dihydroxystearate compounds (2) give coloured products on saponification; but carbonyl derivatives (3), particularly α-unsaturated keto-compounds,

Table III.

Products from the distillation of autoxidised C_{18} unsaturated methyl esters.

Initial palm oil methyl esters: I.V. 51·1.
„ C_{18} methyl esters: I.V. 93·9.
(Stearate 6·8%, oleate 77·2, linoleate 16·0%).

Remarks: all distillations.

Autoxidation no.	4	5
Conditions	Aeration for 12 days at 55° C_{18}	Aeration for 12 days at 55° C_{18}
Distillation: methyl esters		
Peroxide at time of distillation:		
Lea value	195	187
Milliequiv., %	39	37
Hydroperoxide, % wt.	6·4	6·1
Total wt. distilled, kg.	4·8	3·5

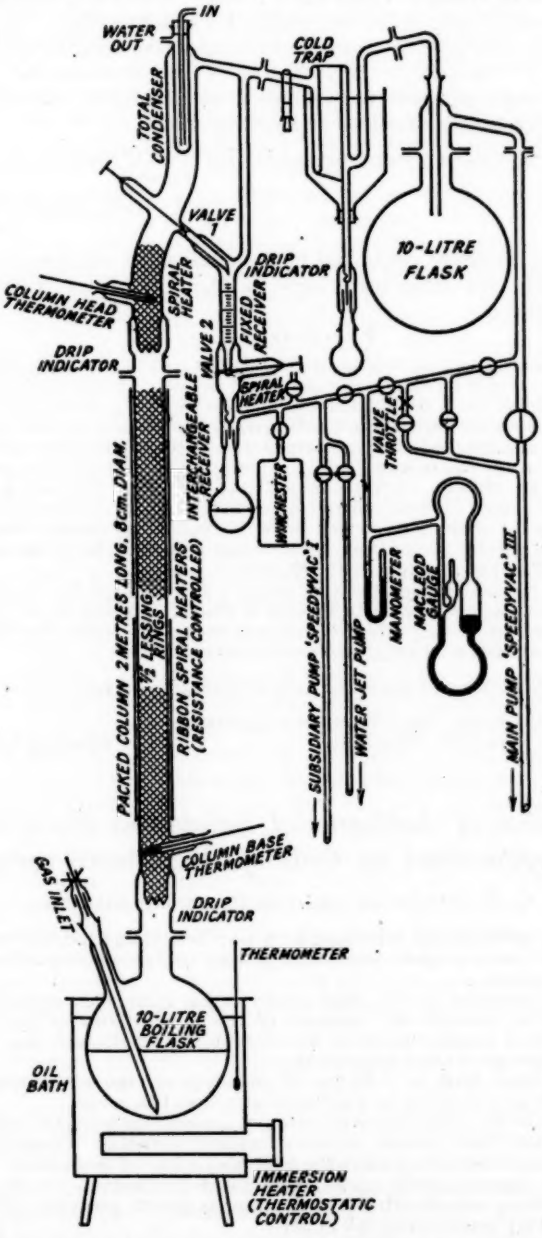
Distillate no.	Quality.	Colour.	Colour on saponification.	Light absorption.	Smell.
1	Vapours condensable in cold trap; two layers, water and oil	Yellow	Very dark brown	Strong 270 mμ max.	Very strong: characteristic of the lower fatty aldehydes
2	B. p. 94—122°/1 mm.	Yellow	Very dark brown	Strong 270 mμ max.	Strong, greasy
3	Recovered esters, b. p. 160°/1 mm.	Colourless	Very pale yellow	Very weak	None
4	End distillate	Yellow	Brown	Strong 270 mμ max.	Slight
5	Column extract	Brown	Brown	Strong	Slight
6	Slightly viscous residue	Brown-yellow	Brown-yellow	Strong	Slight, like castor oil

Autoxidation no.	4.			5					Wt. % according to I.V. and SCN val.		
Distillate no.	Wt., %.	I.V.	Sap. value.	Wt., %.	I.V.	SCN val.	Sap. value.	Setting point.	Stearate.	Oleate.	Linoleate.
1	0·52	69·3	224	0·71	43·1	—	220	—	—	—	—
				(Water) 0·09							
2	1·49			4·46	60·4	—	222·5	—	—	—	—
				(a) 13·02	74·6	61·5	192·5	14°	28·5	56·3	15·2
				(b) 13·56	75·1	68·9	191	14·8	19·7	73·1	7·2
				(c) 13·08	75·3	68·5	191	14·3	20·2	71·8	8·0
3	77·66	76·0 (middle fraction) 78·8		(d) 12·66	73·8	66·5	189·5	17·2	22·6	68·9	8·5
				(e) 14·75	70·8	57·2	190	19·8	33·5	50·6	15·7
				(f) 10·00	61·8	49·3	189	22·6 / 24·8	42·7	42·8	14·5
4	7·04	58·1	186·5	6·17	59·9	—	188·5	—	—	—	—
5	1·82	58·4	214	2·79	61·1	—	207·5	—	—	—	—
6	8·83	63·7	199·5	8·71	65·3	—	202	—	—	—	—
				(Start of distillation)	71·5						
				(After d)	65·0						

could be responsible for discoloration by auto-condensation (Type C III). The present investigation on heated autoxidation products indicates that a considerable degree of the darkening is due to aldehydes produced by fission (Type B II); but the darkening of the distillation

FIG. 10.

High-vacuum still with 10-litre boiling flask and efficient reflux column.



residue suggests the presence therein of other ketonic substances unstable to alkali. Bergstrom (*loc. cit.*) has identified a yellow product, probably an $\alpha\gamma$-diunsaturated ketone, from methyl linoleate, and he attributes this to the dehydrative action of alumina on the initial hydroperoxide. A similar change may have taken place in the present experiments, as water was always obtained

in the early stages of distillation (Type B I internally; cf. Robertson and Waters, *Trans. Faraday Soc.*, 1946, **42**, 201; Waters, Faraday Society Discussion 1947, " The Labile Molecule "). The systematic theoretical treatment of these reactions given earlier indicates that a most probable source of keto-compounds lies in the activation of a tertiary carbon atom [Fig. 4 (*d*) and (*e*); Treibs, *Ber.*, 1944, **77**, 69] which is most likely to arise in a conjugated system. The product of such an activation, a tertiary-carbon hydroperoxide, immediately gives, on reduction, a keto-group by keto-enolic change (Types A, B I, B IV, C IV) and in some circumstances an α-keto-hydroxy-compound (Types A III internally, B III internally). The linoleic methylene hydroperoxide [Fig. 4 (*b*) and (*c*)], by reacting with an active tertiary carbon group, can give an α-ketol or enediol (A IV internally). Morrell *et al.* (*Trans. Faraday Soc.*, 1942, **38**, 862) prove the presence, in autoxidising conjugated compounds, of pseudo-acidic α-keto-hydroxy-compounds which form dark yellowish-brown solutions on saponification :

$$\underset{\text{α-Ketol.}}{H\cdot X_6\cdot CH{:}CH\cdot CH(OH)\cdot CO\cdot X_7\cdot CO_2Me} \rightleftharpoons \underset{\text{Enediol.}}{H\cdot X_6\cdot CH{:}CH\cdot C(OH){:}CH(OH)\cdot X_7\cdot CO_2Me} \rightleftharpoons \underset{\text{α-Ketol.}}{H\cdot X_6\cdot CH{:}CH\cdot CO\cdot CH(OH)\cdot X_7\cdot CO_2Me}$$

Dimeric products are no doubt contained in the distillation residues, but whether they are of the ether (Type B III), the ether ring (Type A II), or the ester (Types B IV, C I) types, requires further investigation.

Experimental.

The above hypothesis was developed in order to explain the results obtained in the course of numerous autoxidation experiments carried out as briefly described below. Practical observations are recorded in Table III for products from the autoxidation and distillation of C_{18} unsaturated methyl esters.

For the autoxidations, a current of air was bubbled daily (for 8 hours in diffused daylight) through a tall bottle, containing the unsaturated ester, immersed in a water-bath at 55—60°.

The fractional distillation of the original palm oil methyl esters and of the autoxidised C_{18} methyl esters was carried out in an efficient, high-vacuum, Pyrex still (Fig. 10) with a 10-litre boiling flask immersed in an electrically-heated (Sunvic-controlled) oil-bath. It had an electrically-heated (resistance-controlled) column, 8 cm. in diameter, packed with ½" porcelain Lessing rings surmounted by a variable-reflux still-head regulated to a reflux ratio of not less than 10 : 1 by a glass valve (Gibson, *J. Soc. Chem. Ind.*, 1939, **58**, 317; *Analyst*, 1945, **70**, 453).

The original palm oil methyl esters were made by treating a neutralised N'dian palm oil with a solution of sodium hydroxide in methanol according to Procter & Gamble Co. and E. W. Eckey (B.P. 567,682). This process has been found to be very efficient and economical and to be less drastic than the usual preparation of the fatty acids and acid-catalysed esterification.

The author wishes to thank his colleagues for helpful criticism and suggestions.

Lever Brothers & Unilever Ltd., Research Department,
Port Sunlight, Cheshire. [*Received, February 19th*, 1948.]

---

462. *The Absorption of Antibacterial Substances (2 : 8-Diaminoacridine and Methylene-blue) by Cells of* Bact. lactis ærogenes.

By A. R. Peacocke and Sir Cyril Hinshelwood.

The amount of the antibacterial substance 2 : 8-diaminoacridine (proflavine) taken up from solution by cells of *Bact. lactis ærogenes* gives when plotted against concentration an " absorption isotherm " of sigmoid shape.

Cells trained to be resistant to the drug absorb rather more than untrained cells. Thus adaptation seems not to involve any decrease in the permeability of the cell. A similar conclusion is derived from measurements of the absorption of methylene-blue, with which the isotherm approximates more to the Langmuir type.

A change of pH from 6·16 to 6·96 has little effect on the absorption of proflavine, although the inhibitory action of the drug varies greatly over this range.

Of the constituents of the normal growth medium, ammonium sulphate has no effect on the absorption of proflavine, but glucose causes a marked decrease. Consistently with this, increased glucose concentration antagonises the inhibitory effect of proflavine. Washed cells of different ages absorb approximately equal amounts of proflavine. In the actual growth medium, however, dividing cells absorb less of the drug as growth proceeds, this decrease being principally due to the very considerable fall in pH.

The absorption of proflavine is approximately constant throughout the lag phase of the cells, showing no sudden decrease when division sets in.

The relationship between the lag caused by the drug and the amount absorbed is discussed, and an explanation of certain previous observations is advanced.

From the various competitive effects certain characteristics of the cell surfaces or interfaces which absorb glucose, hydrogen ions and proflavine cations may be inferred.

(1) *Introduction.*—Previous investigations made in this laboratory on the action of anti-bacterial agents upon *Bact. lactis ærogenes* have been partly concerned with the relationships between the concentration in the nutrient medium and the nature and extent of the inhibitory action. The drugs, however, cannot exert their effect until they have either entered the cell or been adsorbed on its wall. The magnitude of their effect should therefore be more directly related to the amount taken up by the cell than to the concentration in the medium.

For proflavine, methylene-blue, and other drugs, functions, $\phi(m)$, of the concentration, m, of the antibacterials have been defined to represent the relationships between m and the decrease in activity of certain inhibited enzymes (Pryce, Davies, and Hinshelwood, *Trans. Faraday Soc.*, **1945**, **41**, 163, 465, 778; Pryce and Hinshelwood, *ibid.*, in the press). One theory regards training as the quantitative expansion of certain enzymes and provides a basis for the calculation, the function ϕ being determined by comparison with experiment. It would be of interest to discover how ϕ and related quantities depend on the amount of drug actually taken up by the cell, since this might provide more direct information about the nature of drug action.

Determinations of the amount of drug absorbed by a given mass of cell material could also throw light on another aspect of the adaptive process, namely, the possibility of modifications in the organism whereby the trained cells take up less of the antibacterial than the untrained strain. York, Murgatroyd, and Hawking (*Ann. Trop. Med. Parasit.*, **1931**, **25**, 351; see also Hawking, *J. Pharm. Exp. Ther.*, **1937**, **59**, 123) found that strains of trypanosomes trained to withstand the inhibitory action of various arsenical compounds, absorbed little or none of these substances. This behaviour was in marked contrast to that of normal trypanosomes which absorbed all the available drug from solutions of similar concentration.

Another characteristic of the action of acridine drugs about which determinations of absorption could provide useful information is the dependence of activity upon pH. McCalla (*J. Bact.*, **1940**, **40**, 23; **1941**, **41**, 775) has described experiments on the competitive absorption of hydrogen ions, metallic cations, and the cations of basic drugs (such as methylene-blue and crystal-violet) by washed suspensions of *Bact. coli*, *B. bellus*, and *Corynebacterium simplex*. The results of his work which concern us here are: (i) cationic drugs, such as methylene-blue, replaced the hydrogen ions absorbed by cells previously washed with dilute acid, and (ii) the number of gram-equivalents of hydrogen ions and drug cations (*e.g.*, crystal-violet) absorbed by a given mass of cellular material showed an inverse relationship over the pH range studied (*Stain Technology*, **1941**, **16**, 95).

(2) *Scope of the Experiments.*—The complete absorption isotherm of cells untrained to proflavine was determined and found to be of a sigmoid shape, the uptake per cell reaching a limit above concentrations of 250 mg./l. The isotherm for methylene-blue, however, was found to be of the usual Langmuir or Freundlich type, and this suggested that the precise shape of the curve was conditioned rather by the properties of the drug employed than by the special relation of drug and cell. As regards their drug action, methylene-blue and proflavine are known to act on the same or related systems within the cell, and this idea proved to be consistent with the similarity in the relationship between the lag and the amount of drug absorbed, in the two cases.

The absorption isotherms of cells previously trained to proflavine were of the same sigmoid shape, but the absorptions were, on the average, about 20% greater than with untrained cells. The relationship between the lag of trained cells and the amount of drug absorbed was determined, and the shape of the isotherm was found to explain certain previous observations on the behaviour of cells trained to high concentrations of proflavine.

Over the pH range 6·16—6·96 the absorption of proflavine was found to be constant. The results merit discussion in the light of the known wide variation of inhibitory effect of proflavine with pH in this range.

Over a period of 6 hours near the end of growth, there is little change in the amount of proflavine absorbed by each cell from buffered saline. With growing cells in the nutrient medium there is a decrease in absorption from the start of growth to the end of the logarithmic phase. This decrease is principally due to the very considerable fall in pH.

Ammonium sulphate has little effect on the absorption of proflavine by resting cells, but glucose causes a marked decrease. Consistently with this, increased glucose concentration is found to antagonise the effect of proflavine on lag.

From the various competitive effects certain characteristics of the cell surfaces or interfaces which absorb glucose, hydrogen ions and proflavine cations may be inferred.

The absorption of proflavine was found to be approximately constant throughout the lag phase. There was no sudden decrease when division started.

(3) *Experimental Method.*—The solutions from which the drug was absorbed by resting cells

varied in different experiments, but the basic technique was as follows (variations from this will be described in the appropriate sections). About 2 l. of a culture of *Bact. lactis ærogenes* growing at 40° in an aerated synthetic medium of glucose, ammonium sulphate, phosphate buffer, and magnesium sulphate were centrifuged for 15 minutes at 6000 r.p.m.; the population then corresponded to about 600 million cells/ml. The filtrate was discarded, and the cells washed with saline (9 g./l.) and centrifuged again. The process was repeated twice more, after which the cells were suspended in a small volume of saline (or phosphate). This suspension was aerated for about 30 minutes to break up any adhering masses of cells, and its volume was then adjusted until it had a count of 1—3 $\times$ 10^9 cells per ml.

10 Ml. portions of the suspension were then transferred to 6-in. $\times$ 1-in. test tubes containing solutions composed of:

10 Ml. of a 9 g./l. solution of potassium dihydrogen phosphate to which 4N-sodium hydroxide had been added to bring its pH to the desired value (or 10 ml. of saline, having dissolved in it the substance the effect of which was to be studied).

x Ml. of a 1000 or 2000 mg./l. solution of proflavine sulphate, x varying from 0·1 to 5 ml.

$(5 - x)$ Ml. of saline.

The test tubes were then placed in a thermostat at 40°, in order to reproduce the conditions obtaining in growth experiments, and gently aerated to keep the mixture stirred until equilibrium had been reached (see below). The solutions were next centrifuged for 20 minutes and the supernatant liquid carefully removed by means of a pipette. The concentration of proflavine in these solutions was determined by measurement of their light absorption with a Spekker photoelectric absorptiometer (cobalt-glass filter) previously calibrated against solutions of known concentration. From the results and from a knowledge of the original proflavine concentration the amount taken up by the cells could be calculated.

The number of cells per ml. of the suspension was determined by the counting under the microscope of a suitably diluted sample in a Thoma hæmocytometer. Number per ml = $1{\cdot}25 \times 10^6 \times n_H$, where n_H = hæmocytometer reading.

The Spekker instrument was also used as a nephelometer to measure the turbidity of the suspensions. It was first calibrated with samples of a culture at different stages of its growth and of determined hæmocytometer count (this varied over the range 20—1000 million/ml.). A series of pieces of brass, in which holes of rectangular cross-section had been cut, were used as standard screens. The calibration curves could then be used to determine counts of other suspensions. Since the method gives primarily the quantity of light-scattering bacterial substance in a given volume, the " count " so determined, n_s, will only be in direct proportion to n_H for suspensions in which the cells are of constant size. The quantity n_s/n_H should be a measure of the bacterial mass per single cell.

Final results were normally expressed by dividing the decrease in drug concentration (mg./l.) in a given solution by n_H or n_s and multiplying the respective quotients by 1000. This gave two quantities A_H and A_s. A_H proved the most satisfactory quantity to employ, the chief reason for this being the observed steady decrease with time of n_s for a given suspension.

(4) *Absorption of Drugs by Untrained Cells.*—(a) *Proflavine.* It was first necessary to find the length of time taken for the proflavine to be fully absorbed. Experiments were therefore made in which, at varying intervals after the addition of the bacterial suspension to a series of constant drug–saline–buffer solutions, successive tubes were centrifuged and the residual concentration of proflavine determined. It was found that in more than 10 and in less than 30 minutes this concentration had reached its minimum value, thereafter remaining constant.

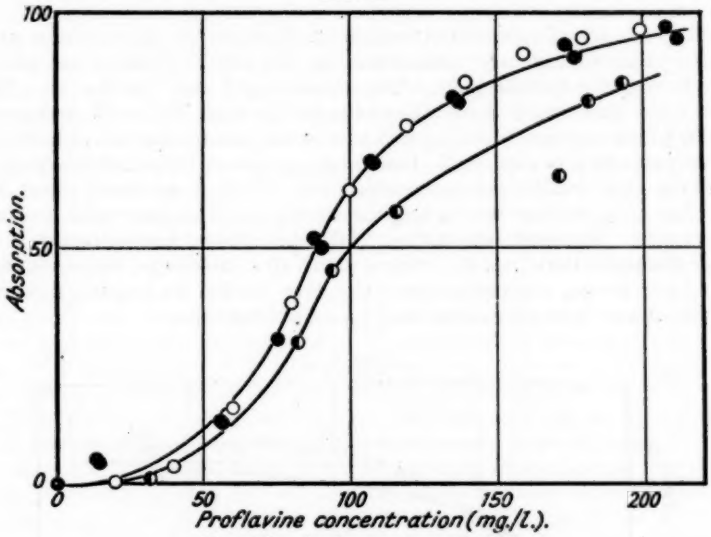
This preliminary experiment shows that a time of contact of 90—120 minutes is fully adequate for equilibrium to be established and was the interval employed.

The complete absorption isotherm of cells untrained to the drug was then determined a considerable number of times. Typical results are shown in Fig. 1 where A_H is plotted against the concentration of proflavine in the supernatant liquid. The curves are seen to be of a sigmoid type, the absorption reaching a limiting value at concentrations of about 200—250 mg./l. The point of inflection occurs at about 65—85 mg./l. An average variation in the position of the isotherms of $\pm$10 units of A_H (as measured at the upper end of the curves) was observed. The curves obtained by plotting A_s against drug concentration showed laregr differences, the reason for which will be discussed later.

Despite the variation in the limiting values of A_H, the general shape, the proflavine concentration at which the inflection occurred and the concentration at which the limit was approached did not vary to any marked extent. To illustrate this graphically, and also to obtain an average isotherm, the following procedure was adopted. A table was made of the

limiting values of A_H in the seven experiments with normal cells and the average value, p, was calculated. The individual limiting values in the various experiments being $q_1, q_2, \ldots q_n \ldots$, the experimental values of A_H at each point on any isotherm were then multiplied by the appropriate

FIG. 1.

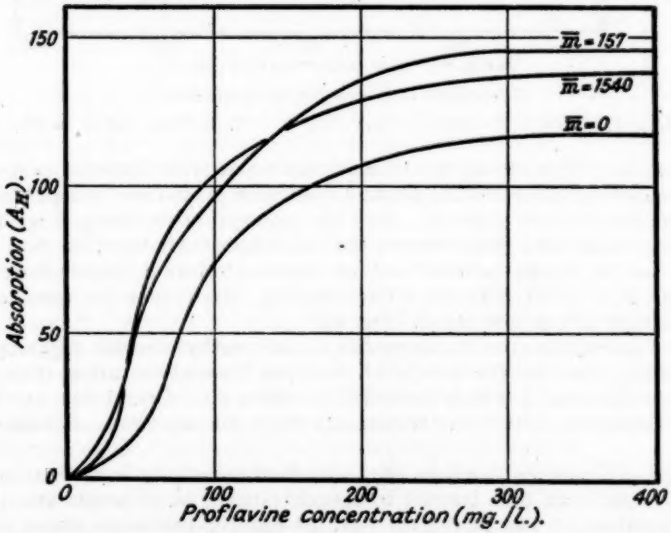


Absorption isotherms, normal cells:

Black circles, experimental, series 1.
Open circles, calculated from $A = Scm^4/(1 + cm^4)$ *with* $c = 1{\cdot}52 \times 10^{-8}$.
Half-black circles, experimental, series 2.

FIG. 2.

Absorption isotherms (average) for trained and untrained cells. $\bar{m}$ = *training concentration.*



factor p/q_n, whereby all the curves are scaled to come to the same (average) limiting value. The reduced curves were substantially similar, and a mean value is plotted in Fig. 2 ($\bar{m} = 0$).

According to Figs. 1 and 2, the absorption isotherm is concave upwards over the range of concentration of 0—70 mg./l. As this part is of special interest, a more detailed study of it was made, the experiments providing the data for the study of the relationship between lag and A_H (see Discussion).

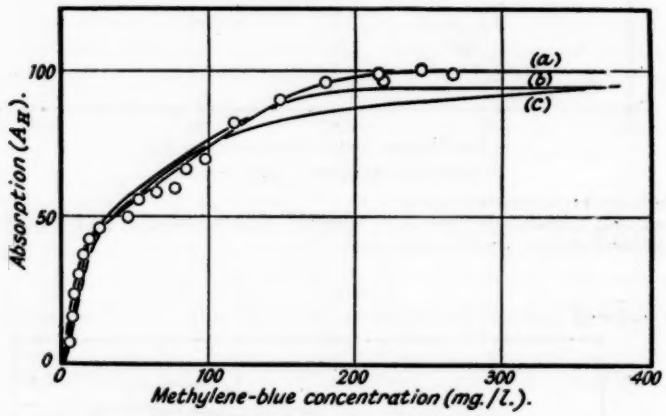
The chief characteristic of the isotherm is the sigmoid shape with its point of inflection at about 65—85 mg./l. Fig. 1 shows that the curve is described by the following equation

$$A_H = S\left\{\frac{cm^4}{1 + cm^4}\right\}$$

where S and c are constants.

The sigmoid shape might arise from the individual properties of proflavine itself or it might be characteristic of all cationic dye absorption by the cells. Reasons are given in the next section for preferring the former view. The shape could then be due to: (i) A Langmuir adsorption of some associated form of proflavine present in small proportions and the concentration of which is proportional to a power of the total drug concentration greater than unity. It is not easy on this view to see how a large polymeric form of the drug could be more easily absorbed than the smaller monomer molecules. (ii) A co-operative effect, the presence of adsorbed molecules on given sites facilitating the adsorption of similar molecules on neighbouring sites (see Brunauer, " Physical Adsorption ", Oxford, 1943; Hinshelwood, " The Chemical Kinetics of the Bacterial Cell ", p. 6). Since many dye molecules, including aminoacridines, are known to have strong intermolecular attractive forces, an explanation of the sigmoid isotherm in terms of a co-operative effect seems a quite likely one.

FIG. 3.



Absorption isotherms for methylene-blue :

(a) $\bar{m} = 0$, *typical experimental curve*; (b) $\bar{m} = 0$, *average*; (c) $\bar{m} = 150$ *mg./l.*

(b) *Methylene-blue.* The absorption of methylene-blue from buffered saline by *Bact. lactis ærogenes* at 40° was determined by the method used with proflavine (except that a yellow filter was employed in the Spekker instrument). The absorption isotherm (Fig. 3) approximates rather more closely than with proflavine to the usual Langmuir type, in spite of the fact that methylene-blue can be highly polymerised in aqueous solution (Rabinowitch and Epstein, *J. Amer. Chem. Soc.*, 1941, **63**, 69). The limiting absorption is approached when the concentration exceeds about 200 mg./l. (Fig. 3).

The difference between the results for proflavine and methylene-blue suggests that the curves are specifically determined by the nature of the dyes themselves rather than by an inherent property of the mechanism by which the cell takes them up. Once taken up the two dyes are known to act in similar ways (Pryce, Davies, and Hinshelwood, *Trans. Faraday Soc.*, 1945, **41**, 465).

(5) *Absorption of Drugs by Trained Cells.*—(a) *Proflavine.* An investigation similar to the above was carried out with cells trained to concentrations, $\bar{m}$, of proflavine of 157, 312, and 1540 mg./l., respectively. The isotherms were of exactly the same shape as those for the untrained cells, but the values of A_H were somewhat higher. Some averaged results are plotted in Fig. 2. These curves show that in this example resistance to the action of proflavine is not due to a decrease in the permeability of the trained cells, since in actual fact they absorb rather more of the drug after training than before (cf. the results of Hawking, *J. Pharm. Exp. Ther.*, 1937, **59**, 123; Fischl, Kotbra, and Singer, *Z. Hyg. Infectionskrankh.*, 1934, **116**, 69; Stearn, *J. Bact.*, 1927, **14**, 349; Deere, *ibid.*, 1939, **37**, 473).

(b) *Methylene-blue.* The absorption isotherm of methylene-blue was determined for cells trained to 150 mg./l. of the drug [Fig. 3, curve (*c*)]. It is seen to approximate closely, within the experimental error, to the average absorption isotherm of the untrained cells [curve (*b*)]. In the case of methylene-blue, it is therefore also clear that adaptation to the drug does not involve any obvious decrease in permeability.

(6) *Influence of pH on the Absorption of Proflavine.*—For the investigation of the effect of changed pH on the take-up of proflavine it was first necessary to determine whether the light absorption of the latter would be at all influenced by the altered conditions. According to the results of Albert and others (*Brit. J. Exp. Path.*, 1945, **26**, 160) it should not, since, over a wide range of pH, the drug is completely in the form of univalent cations.

A series of phosphate buffers was made, and to equal volumes of each of these were added equal volumes of a solution of proflavine sulphate. The concentration of proflavine in each solution was then measured by means of the Spekker instrument and the previously determined calibration curve. Over the pH range 5·5 to at least 7·6 the expected value was found. But in more acid buffers the instrument indicated too great a concentration. The reason for this is uncertain. From the practical point of view, however, it follows that the calibration curve may be used over the pH range 5·5 to 7·6.

Absorption isotherms were then determined for various standard suspensions of untrained cells in a series of solutions only differing from those employed in the experiments of the previous section in the pH of the buffers. An attempt was made to cover the pH range 3 to 7·6, but this was rendered difficult (i) because at the lower end the buffers lack the capacity to deal with the acid arising from the hydrolysis of proflavine sulphate, and (ii) by the uncertainty in the proflavine determination already mentioned.

Over the range 6·16—6·96 the pH proved to have very little effect on the absorption of the drug. Indeed, only one sigmoid curve could be drawn through all the experimental points obtained in this range. At pH 4·78, 5·49, and 5·77 the limiting values of A_H were found to be lower than those obtained in the higher range. The main results are summarised in Table I.

TABLE I.

Influence of pH on the limiting value of A_H.

pH.	Lt. A_H.	pH.	Lt. A_H.	pH.	Lt. A_H.	pH.	Lt. A_H.
4·78	44	6·16	110	6·47	110	6·77	100
5·49	68	6·20	100	6·48	90	6·96	110
5·77	80	6·32	110	6·54	100	6·97	106
6·04	100	6·39	100	6·69	110	—	—

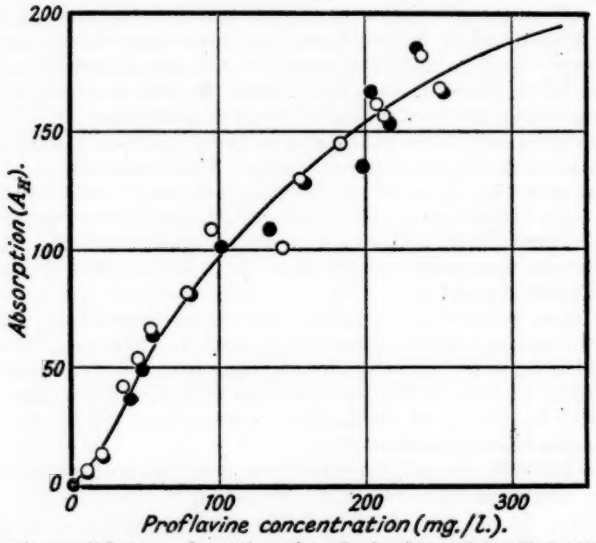
Stearn and Stearn in a series of papers (*e.g.*, *Protoplasma*, 1931, **12**, 435, 580) have measured the "iso-electric zones" of various organisms. This zone is the pH range within which the absorption of acidic (anionic) and basic (cationic) dyes is of the same order. Above it only cationic dyes are absorbed to any extent, and below it only anionic dyes. Gram-positive organisms were found to have iso-electric zones around pH 2·0, and Gram-negative organisms, of which *Bact. lactis ærogenes* is an example, around pH 5·0. The value given for *Bact. lactis ærogenes* is 5·2. At pH's about one unit greater than the iso-electric point, a limiting value of the absorption of cationic dyes is attained (see Stearn and Stearn, *J. Bact.*, 1924, **9**, 463; Dubos, "The Bacterial Cell", 1945, Harvard, Chap. III). The results of the present investigation are seen to be in accord with these studies. Over the pH range 6·16 to 6·96, where its total absorption by the cell has been seen to change very little, there is a 2·5-fold variation in the lag caused by the proflavine (Peacocke and Hinshelwood, this vol., p. 1235). This suggests that the centres where proflavine cations cause lag and where also they are in competition with hydrogen ions are only a small fraction of the total which are capable of absorbing proflavine, under the conditions of resting-cell experiments.

(7) *Effect of Medium Constituents on the Absorption of Proflavine.*—(a) *Ammonium sulphate.* Cells were suspended in the phosphate buffer (pH 7·12) and 10 ml. of this suspension were then added to the absorption solutions containing, besides the usual x ml. of proflavine solution and $(5 - x)$ ml. of saline, 10 ml. of a 5 g./l. solution of ammonium sulphate in saline. The final difference from the previous procedure is thus that the absorption solutions contain ammonium sulphate. The same cell suspension was also added to a similar series of solutions containing no ammonium sulphate.

The two absorption isotherms (Fig. 4) obtained were identical. Ammonium sulphate thus has no effect on the absorption of proflavine by the cells.

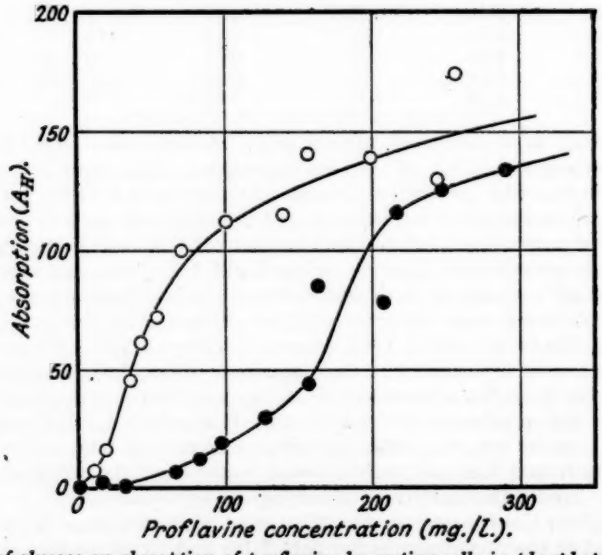
(b) *Glucose.* A similar series of experiments was carried out with glucose (20 and 40 g./l.) in place of ammonium sulphate. The absorption of proflavine was consistently less in the presence of glucose. Fig. 5 shows a typical pair of curves. The two concentrations of glucose,

FIG. 4.



Effect of ammonium sulphate on absorption of proflavine by resting cells in phosphate–saline:
Open circles, without ammonium sulphate.
Black circles, with 2 g./l. ammonium sulphate.

FIG. 5.



Effect of glucose on absorption of proflavine by resting cells in phosphate–saline:
Open circles, without glucose.
Black circles, 20 g./l. glucose.

one double the other, only gave a 10% difference in effect, which is about the variation observed with the same strain of cells under apparently identical conditions.

(c) *Complete growth medium.* Since the concentrations of proflavine employed in these absorption experiments are mostly very much higher than that needed (54 mg./l.) completely to

inhibit the growth of untrained bacteria in the normal growth medium, it was possible to determine the isotherm in a complete medium without multiplication of the cells. The absorption was lower than that in saline–phosphate by approximately the amount to be expected from the glucose present.

(8) *Influence of Glucose on the Lag induced by Proflavine.*—In the light of (b) and (c) of the last section it was thought to be of some interest to investigate whether or not differences in the concentration of glucose can cause corresponding changes in the lag due to the drug.

The lag was therefore determined as a function of proflavine concentration in two series of experiments carried out in the usual way, except that the media contained two different concentrations of glucose, namely 3·85 g./l. and the usual amount, 38·5 g./l. The higher concentration of glucose was found to reduce the lag over the whole range of proflavine concentrations (Table II).

TABLE II.

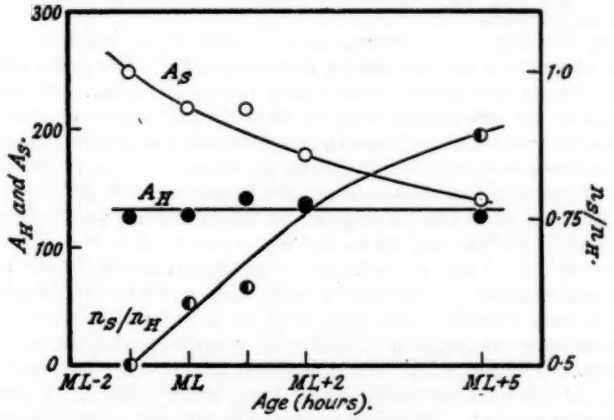
Influence of glucose on the lag induced by proflavine.

Concn. of proflavine (mg./l.).....	0	10	20	30	40	45	50	55
Lag in presence of 3·85 g./l. of glucose minus lag in 38·5 g./l. (mins.)	0	0	40	250	800	1040	1380	∞

(9) *Variation of Proflavine Absorption with the Age of the Cells.*—(a) *Absorption by centrifuged and washed cells of varying age.* Preliminary experiments indicated that there was an appreciable

FIG. 6.

Variation of A_S, A_H, *and* n_S/n_H *with age at time of centrifuging.*



difference between the amount of proflavine absorbed by cells centrifuged immediately the parent culture had ceased to divide, and those obtained by centrifuging 24 hours later. It was therefore thought worth while to study this effect further. The procedure was as follows:

2500 Ml. of complete medium (I) were inoculated with untrained, normal cells, and when the count of the growing culture had reached 3—7 × 10^8 per ml. the cells were centrifuged and washed. The absorption isotherm was then determined. This stage in the growth of the parent is about 1 hour before division ceases (the point at which the lag of an inoculum from it into a fresh medium would be minimal).

The whole process was repeated when the culture reached the minimum lag stage (time denoted by ML), and also at $(ML + 1)$, $(ML + 2)$, and $(ML + 5)$ hours. Another quantity (II) of complete medium was similarly inoculated, and this was centrifuged and tested at ages of $(ML + 10)$, $(ML + 20)$, $(ML + 44)$, and $(ML + 140)$ hours.

With culture (I), Fig. 6 shows that the limiting value of A_H does not vary to any great extent from $(ML - 1)$ to $(ML + 5)$ hours, any differences being within the experimental error. The limiting value of A_S over this range, however, decreases steadily. Thus the amount of proflavine absorbed by each cell does not alter over the period $(ML - 1)$ to $(ML + 5)$, whereas that absorbed per unit bacterial mass decreases. This implies that the mass per cell increases from $(ML - 1)$ to $(ML + 5)$. This is shown in the figure by the trend in the ratio n_S/n_H which is approximately proportional to the mass of each cell. Later on it is shown to decrease since the cells in old cultures are smaller than the average.

With culture II, Table III shows that from $(ML + 10)$ to $(ML + 140)$ the limiting values of both A_H and of A_S decrease steadily. This is not unexpected since at great ages general degeneration of the cell substance must occur.

TABLE III.

Variation of proflavine absorption with age (washed cells).

Age at time of centrifuging:	$(ML + 10)$.	$(ML + 20)$.	$(ML + 44)$.	$(ML + 140)$ hrs.
Lt. A_S	190	165	135	110
Lt. A_H	171	139	120	77
n_S/n_H	0·88	0·73	0·84	0·69

(Since A_H and A_S are calculated by dividing the same concentration decrease by the appropriate values of n_H or n_S, A_H/A_S is equal to n_S/n_H.)

In these experiments the absorption by washed cells of varying age, free from their growth medium, is measured. Thus any effects that substances such as medium constituents, metabolic products, or acids from fermentation might have on the absorption have been eliminated. The constancy of the amount of drug absorbed per cell over an age range of 6 hours about the minimum lag stage (Culture I) is therefore of special interest. It shows that any variation in the absorption of proflavine in an actual culture between the ages of $(ML - 1)$ to $(ML + 5)$ hours must be due to the presence of diffusible substances in the medium and not to changes in the structures responsible for the absorption.

The variation of A_S with age (Culture I) explains the variation often observed in the A_S-isotherms of cells, centrifuged *approximately* at the minimum lag stage, and is a further reason for plotting A_H-isotherms.

(b) *Absorption by dividing cells at various ages.* It seemed of interest next to find a method of determining the absorption of cells during actual growth. The chief difficulty in this is to ensure that the cells do not multiply further during the centrifuging. At first this was done by adding formaldehyde to the absorption solution immediately before separation. Control tests, however, showed that the whole principle of the experiment was invalid, the apparent absorption of resting cells in saline–phosphate being greatly increased by the presence of formaldehyde, possibly as a result of chemical reaction between the proflavine and the formaldehyde.

Growth of the cells can, however, be stopped by the proflavine itself, since concentrations of 60 mg./l. are sufficient to do this and up to 400 mg./l. are used in the absorption experiments. In deciding the technique of the experiment it is important to know the time taken for equilibrium to be established. With resting cells this is 10 to 30 minutes [Section 4 (a)]. Experiments of S. Jackson (unpublished) show that for growing cells there is also an interval of about 20—25 minutes between addition of proflavine solution and cessation of growth which is, moreover, quite sharp. The procedure was, therefore, as follows: Two portions of 24 ml. each were taken from 1 l. of the growing culture, and 1 ml. of an 8000 mg./l. solution of proflavine sulphate was then added to each. They were aerated at 40° and, after not less than 25 minutes, to ensure that division had ceased, a sample was taken and the solution then centrifuged in the ordinary way.

A sample taken when the drug was first added gave a point on the growth curve of the culture and thus its age. A second sample gave the count (n_H) in the absorption solutions immediately before centrifuging.

From these and other determinations plots of the following against the age of the culture were obtained: (i) Cell count, (ii) A_H, (iii) A_S, (iv) pH of the medium. These curves are shown in Fig. 7. It is seen that, at first, the values of A_H and A_S are considerably higher than with the resting cells in phosphate–saline, but that the values of both decrease rapidly as growth proceeds and reach a minimum shortly after it stops. The decrease runs parallel with the drop in the pH of the supernatant liquid which is quite sufficient to account for it, as may be judged by continuing Table I below the pH value of 4·78.

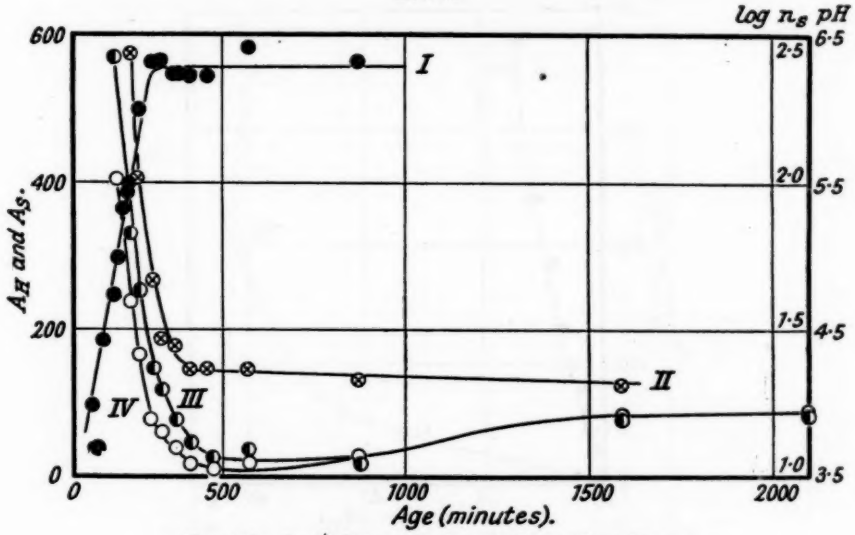
This change in absorption as growth proceeds throws light on a phenomenon previously observed in the laboratory (Davies, Hinshelwood, and Pryce, *Trans. Faraday Soc.*, 1944, **40**, 397). If cells untrained to proflavine are grown in its presence and removed after one or two divisions, they are found to have acquired almost complete resistance to the proflavine in a subsequent test made under the same conditions. This resistance is, however, unstable in the sense that one or two subcultures in the drug-free medium completely remove it again. If the cells, instead of being taken out after only one or two divisions, are allowed to complete their growth cycle in the presence of the proflavine, the degree of resistance acquired is very much less. This now

finds an explanation in terms of the result just described. As growth proceeds the uptake of proflavine per cell diminishes rapidly, and, since at this stage the acquired resistance is unstable, a reversion from the initial training takes place.

(10) *Absorption during the Lag Phase.*—Since it has been shown that the absorption of proflavine decreases rapidly during division, it is interesting to discover if there is any variation in absorption during the lag phase and, more important, if it shows any sudden change once cell division begins.

The method used was as follows. 500 Ml. of a culture of untrained cells at the minimum lag stage were centrifuged, washed thrice with saline, and then suspended in it. A calculated volume of this suspension was then added to 500 ml. of complete growth medium containing proflavine at a known concentration of about 30—40 mg./l., so as to give an initial count of about 250 million/ml. The culture was maintained at 40° and aerated. Under these conditions the cells had a lag of about 350 minutes. At intervals, 25 ml. samples were examined. This procedure was continued until after 1—2 divisions had been completed.

FIG. 7.



Absorption by dividing cells in actual growth medium :
Curve I, Growth curve (age–log n_S*). Curve II, Age–pH.*
Curve III, Age–A_S*. Curve IV, Age–*A_H*.*
(Note different scales.)

One set of results is given in Table IV. The proflavine concentration had to be low, or division would not have occurred, and the percentage error in the results is therefore high. Moreover, the count has to be small (about 1/5 normal) in order that one or two divisions may be observed before growth ceases. This further increases the percentage error since it causes the concentration decreases to be very small.

Despite this it its clear from Table IV that the absorption of proflavine does not begin to decrease *immediately* division commences. In fact it occurs some 350 minutes later, by which time one division is almost complete. This shows that the onset of division is not accompanied by any sudden transference of absorbed drug from the cell to the medium.

TABLE IV.

Variation of proflavine absorption in the lag phase.

Age, mins.	n/n_0.	$A_H/16{\cdot}0$.		Age, mins.	n/n_0.	$A_H/16{\cdot}0$.	
45	1·00	0·87		475	1·22	1·00	
148	1·07	0·81		725	1·54	1·15	
210	1·00	1·23		750	1·92	0·45	(A_H begins to decrease)
270	1·03	0·85		780	2·13	0·86	
398	1·06	1·17	(Onset of division)	811	2·20	0·56	

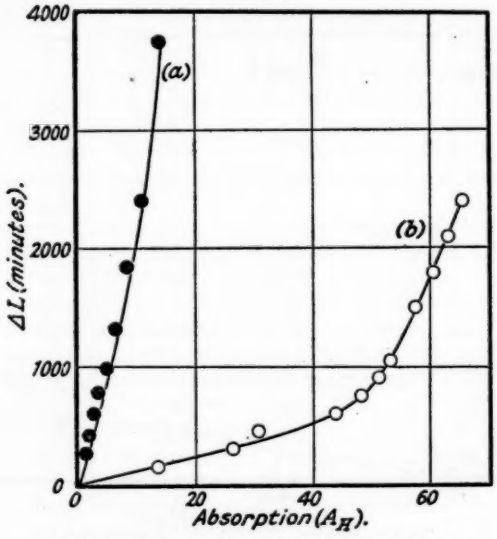
$1{\cdot}25 \times 10^6 \times n$ = Count of the culture at each age.
$1{\cdot}25 \times 10^6 \times n_0$ = Initial count of the culture ($n_0 = 259$).

(11) *Discussion.* (a) *Action of proflavine upon untrained cells.* It is now possible to examine more closely the relationship between the increment in lag (ΔL) due to the presence of proflavine and the amount taken up by the cell (A_H).

The value of A_H for the untrained strain at various concentrations of the drug in the medium is known from the detailed investigations over the range 0—70 mg./l. [Section 4 (a)]. The lag–concentration relation for this strain of cells was determined. The values of ΔL were then plotted against the corresponding values of A_H [Fig. 8, curve (*a*)]. A weakness of this comparison lies in the fact that A_H was determined in buffered saline whereas ΔL was naturally determined in the presence of full growth medium. Experiment has shown, however, that with the latter only the scale and not the shape (*i.e.*, sigmoid character, point of inflexion, and the concentration at which A_H approaches its limit) is altered relative to that obtained with buffered saline.

Thus the general form of the relationships between lag and the absorption of drug should be revealed by the comparison.

FIG. 8.



Relation between lag and drug-absorption:
(a) *Black circles, proflavine.*
(b) *Open circles, methylene-blue.*

The ΔL–A_H relationship for the untrained cells in proflavine is seen to be almost linear over a considerable range. Eventually, however, the lag rises steeply to infinity, as can be seen from Fig. 9. ΔL reaches infinity when the bulk concentration is 54 mg./l., and up to this point the absorption isotherm is convex towards the m axis. Its curvature is less than that of the lag–concentration curve, and it is for this reason that the ΔL–A_H curve is convex towards the A_H axis.

For proflavine, the $\phi(m)$–m relationship is $\phi(m) = fm$ (Davies, Hinshelwood, and Pryce, *Trans. Faraday Soc.*, 1945, **41**, 163, 465, 778) where f is a constant. The relationship between $\phi(m)$ and A_H will therefore be expressed by a curve of sigmoid shape like the isotherm, since $\phi(m)$ is simply a multiple of m. The value of $\phi(m)$ increases steeply as A_H approaches its limiting value of 116 units.

(b) *Action of proflavine upon trained strains.* For a strain trained to 157 mg./l. (Fig. 3) a plot was made of ΔL against A_H in the same way as before. The ΔL–m data were then calculated from the following equation which is known to give the correct values for the strain of *Bact. lactis ærogenes* used in this laboratory (Davies, Hinshelwood, and Pryce, *Trans. Faraday Soc.*, 1945, **41**, 163).

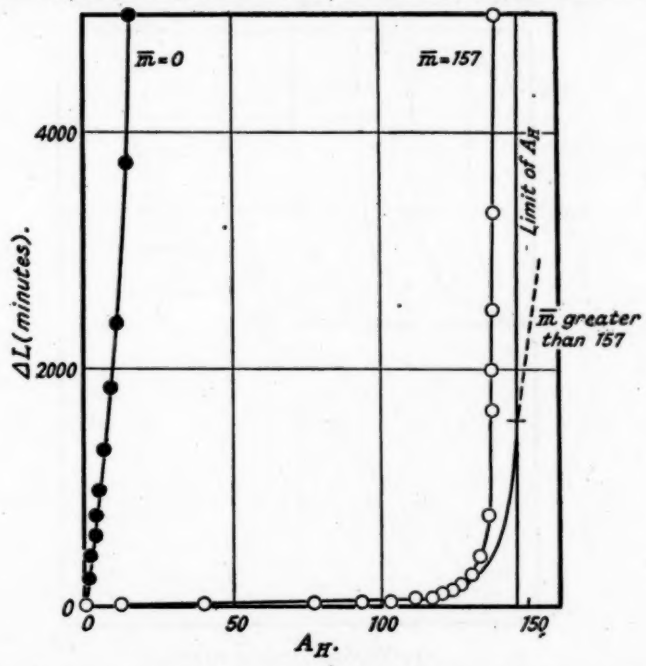
$$\frac{1}{\Delta L} = 10^{-4}\left\{\frac{(\bar{m} + 54)^2}{m} - (\bar{m} + 54)\right\}$$

with $\bar{m} = 157$ mg./l.

The resulting curve, together with that for $\bar{m} = 0$, is plotted on Fig. 9. It should be noted that there is a large range of tolerance to the drug, up to 120 A_H units, and that with quantities of drug in the cell greater than this the lag rises steeply to infinity. The ΔL–A_H curves are limited on one side by the line $A_H = 146$, which is the maximum amount of drug which any cells (trained or untrained) can absorb. As $\bar{m}$ increases above 157, the curves obtained must lie between that for $\bar{m} = 157$ and this limiting line. The experimental evidence shows that with strains trained to concentrations greater than 250 mg./l., the lag–concentration curve at first increases steeply in the normal way until at a certain stage it turns over and becomes horizontal (Davies, Hinshelwood, and Pryce, *Trans. Faraday Soc.*, 1945, **41**, 778, Fig. 2). This means that the ΔL–A_H curves eventually intersect the line $A_H = 146$ at a value of the lag which is a limit for that strain, since no more drug can be absorbed (cf. dotted line in Fig. 9). Further training of such a strain simply causes a progressive decrease in the lag towards zero for all concentrations, *e.g.*, the strain $\bar{m} = 2100$, in Fig. 1 of the paper quoted.

FIG. 9.

Relation of drug absorption and lag for normal and proflavine-trained cells.



The lag–concentration curves begin to become parallel to the m axis when growth is occurring in concentrations of about 250 mg./l. or more, and it is significant that this is precisely the region where A_H reaches its limit. Fig. 10 illustrates this behaviour.

Previous work has shown that *Bact. lactis ærogenes*, when sub-cultured in a concentration, $\bar{m}$, of proflavine, acquires immunity to the action of the drug at all concentrations up to a value which just exceeds $\bar{m}$ itself. The additivity relationships of the type $m_s = \bar{m}$ + constant, where m_s is the concentration of proflavine required to produce a lag of s minutes in a strain trained to $\bar{m}$, begin to break down when $\bar{m}$ is greater than about 200 mg./l. (Davies, Hinshelwood, and Pryce, *Trans. Faraday Soc.*, 1945, **41**, 778). A strain trained at a low value of $\bar{m}$ will not grow at all at $(\bar{m} + 54)$, whereas for $\bar{m} = 450$ the strain will grow in up to 1540 mg./l. (though with increased lag). Further training at $\bar{m} = 1540$ confers practically complete immunity to 3000 mg./l., the highest concentration which it is practicable to use. This can now be explained by the fact that there is a limit to the amount of drug the cell can take up. Training to the lowest concentration (270 mg./l.) at which this maximum is attained gives immunity to much higher concentrations, since these correspond to the same amount of drug absorbed.

(c) *Action of methylene-blue on untrained cells.* From the relationship that, for methylene-blue, $\Delta L = 30m$ (Pryce, Davies, and Hinshelwood, *Trans. Faraday Soc.*, 1945, **41**, 465) and the

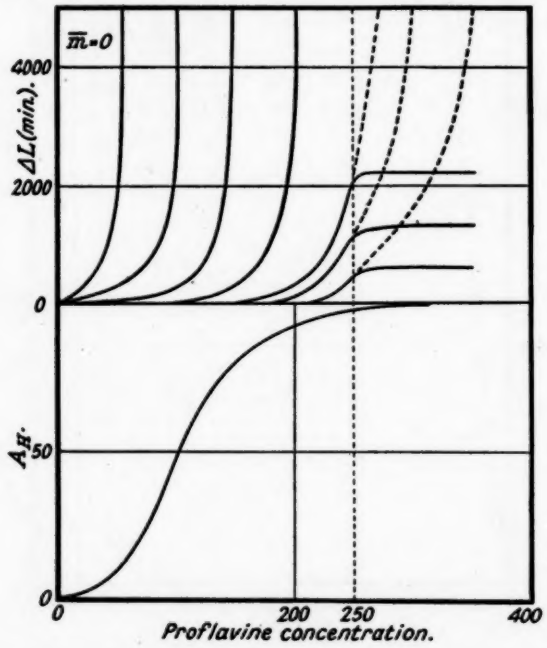
data of the methylene-blue isotherm, the ΔL–A_H curve was plotted [Fig. 8, curve (*b*)]. In spite of the differences in the isotherms and the lag–concentration relationships of the two substances, this curve is seen to be of the same general type as that for proflavine. This is interesting since on other grounds, *e.g.*, the phenomenon of cross-training, the similarity of the mode of action of the two drugs was already known. The differences in their lag–concentration curves are now seen to be due to the superposition of two different absorption isotherms upon two similar ΔL–A_H relationships. The differences in the former may well depend upon differing polymerisation tendencies and different relationships between the spatial configuration of absorbing sites and the structure of the dye.

(d) *Nature of the centres which take up glucose, proflavine, and hydrogen ions.* The competitive phenomena shown by any two of the above species lead to some interesting conclusions. The experimental evidence is as follows.

Proflavine cations and hydrogen ions. These both have positive charges and are probably taken up by negative centres in the cell. At pH below 6 (Table I) the total absorption of

FIG. 10.

Relation between lag, concentration, and drug-absorption for trained strains.



proflavine cations decreases, so that both evidently compete for the same negative sites. From pH 6 to pH 7, however, the total absorption of drug alters little, so that the bulk of the absorbing centres evidently take up the drug in another way in this pH range. A small fraction specially involved in the growth process must, however, continue to absorb hydrogen ions in competition with drug cations, since the lag due to proflavine is still strongly affected by the pH in the direction which this implies (Peacocke and Hinshelwood, this vol., p. 1235; see Section 6).

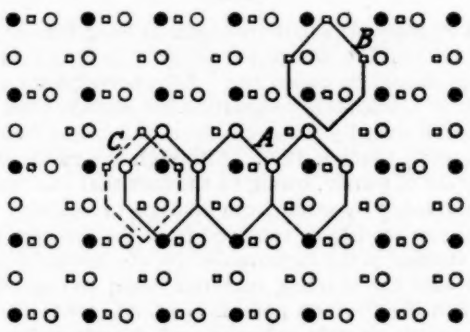
Proflavine cations and glucose. Although these are of a different charge type, the presence of glucose decreases considerably the absorption of proflavine from saline–phosphate [Section 7 (b)]. The glucose must compete with the drug on sites which absorb the large, uncharged rings of the proflavine cations, the proflavine being evidently also absorbed at points other than the charged N atom.* It seems likely, therefore, that the bulk of the proflavine cations are absorbed on a surface consisting of neutral and negatively charged sites in juxtaposition. A change in glucose concentration from 3·85 to 38·5 g./l. affects the lag due to proflavine more than it affects the

* The possibility must not be ignored that the glycolysis which may occur in presence of the glucose provides energy for some unknown process hindering the uptake of proflavine by the cell. But if this were so one would have expected a definite decrease in absorption when active division sets in. This is not observed (Section 10).

absorption of the latter. This again suggests that a small fraction only of the total absorbed proflavine is concerned in the inhibition of growth. This fraction apparently is absorbed on sites more sensitive than the bulk to competition by glucose molecules.

Glucose and hydrogen ions. Over the range 5 to 7·5 (Peacocke and Hinshelwood, *loc. cit.*) the lag in a constant glucose medium is independent of the pH. This indicates that there is no direct competition between the two species.

FIG. 11.



Schematic representation of adsorption sites :

● *Sites for H^+ and proflavine cations.*
○ *Sites for neutral proflavine.*
□ *Sites for glucose.*
A *Proflavine cation.*
B *Glucose molecule.*
C *Site for glucose molecule which could impede the absorption of A, or whose absorption could be impeded by A.*

On the basis of the above evidence a schematic picture of the absorbing surface may be formed and is shown in Fig. 11. The hydrogen being small will be taken up freely in the interstices left by glucose or proflavine. It can prevent the absorption of the latter on certain negative key sites. Glucose and proflavine having large molecules can seriously impede the absorption of one another. Thus sites near the molecule *A* are still available for hydrogen ions while corresponding ones would not be available for glucose on account of the size of the latter.

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, March 4th*, 1948.]

---

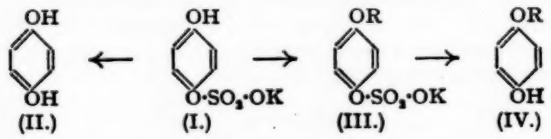
463. *The Elbs Persulphate Oxidation of Phenols, and its Adaptation to the Preparation of Monoalkyl Ethers of Quinols.*

By WILSON BAKER and N. C. BROWN.

Experiments have been carried out in order to determine the most favourable conditions under which alkaline solutions of persulphates attack phenols with free *p*-positions to give quinols, or *p*-substituted phenols to give catechols (Elbs persulphate oxidation). In the former cases it has now been shown that the free phenolic group in the intermediate *p*-hydroxyphenyl potassium sulphates (I) can be alkylated, and the sulphate group subsequently removed by acid hydrolysis, thus providing a route to the synthesis of quinol monoalkyl ethers of known orientation. A reaction mechanism is put forward involving the participation of the sulphate ion radical $\dot{O}{\cdot}SO_3^{\ominus}$.

THE oxidation of monohydric phenols to dihydric phenols by potassium persulphate in alkaline solution was discovered by Elbs (*J. pr. Chem.*, 1893, **48**, 179). If the *p*-position to the phenolic group is free, then quinol derivatives are produced, but if the *p*-position is occupied a derivative of catechol is formed, though usually in much smaller yield. Patents taken out in 1894 (Chemische Fabrik auf Aktien—vorm. E. Schering, D.R.-PP., 81,068, 81,297, 81,298. See Friedländer, " Fortschritte der Teerfarbenfabrikation ", 1894—1897, **4**, pp. 126, 127, and 121 respectively) showed that the reaction proceeds *via* the intermediate formation of a hydroxy-

phenyl potassium sulphate (I), which is subsequently hydrolysed in acid solution to the quinol (II).



This reaction has been erroneously attributed both to Bargellini and to Neubauer and Flatow (see later references), but it should be associated solely with the name of its discoverer, and it is suggested that in future it should be called the " Elbs persulphate oxidation ". It cannot be known as the " Elbs reaction ", since this designation has already been applied to the preparation by the same worker of anthracenes by the cyclisation of 2-methylbenzophenones (see Fieser, in Adams's " Organic Reactions ", 1942, **1**, 129). Although the yields are often low, the products are usually isolated in a state of purity, owing to the fact that the intermediate hydroxyphenyl alkali sulphates are not extracted by ether from alkaline or acidified aqueous solutions, so that the other organic products can readily be removed from the reaction mixture.

The reaction was first studied in the favourable case of *o*-nitrophenol, which gave nitroquinol in 30—40% yield, about half the starting material being recovered. The earliest reactants used by Elbs or described in the German patents (*locc. cit.*) were phenol, *o*-, *m*-, and *p*-cresols, *p*-chloro-, *p*-bromo-, and *p*-nitro-phenols, salicylic acid, *p*-hydroxybenzoic acid, and *o*-, *m*-, and *p*-cresotic acids. The following compounds have been successfully oxidised : salicylaldehyde (Neubauer and Flatow, *Z. physiol. Chem.*, 1907, **52**, 375); 2-hydroxy-4-methoxyacetophenone (Bargellini and Aureli, *Atti R. Accad. Lincei*, 1911, **20**, 118); *p*-hydroxyphenylarsinic acid (D.R.-P., 271,892, 1914); coumarin (giving 6-hydroxycoumarin) and 7-methoxycoumarin (Bargellini and Monti, *Gazzetta*, 1915, **45**, 90); 2-hydroxy-3 : 4-dimethoxyacetophenone (Bargellini, *ibid.*, 1916, **46**, 249; Baker, *J.*, 1941, 667); 2-hydroxy-3 : 4-dimethoxybenzophenone (Bargellini, *loc. cit.*); *m*-hydroxybenzaldehyde (Hodgson and Beard, *J.*, 1927, 2339); 7 : 8-dimethoxycoumarin (Bargellini, *loc. cit.*; Wessely and Demmer, *Ber.*, 1929, **62**, 120); 7-methoxy-8-ethoxycoumarin (Wessely and Demmer, *loc. cit.*); *m*-5-xylenol (Bergel, Copping, Jacob, Todd, and Work, *J.*, 1938, 1383); 2-hydroxy-3 : 4-dimethoxy- and 2-hydroxy-3 : 4-methylenedioxy-benzoic acid, 2 : 3-dimethoxy- and 2 : 3-methylenedioxy-phenol, and 2-hydroxy-3 : 4-methylenedioxyallylbenzene (Baker and Savage, *J.*, 1938, 1602); 2-hydroxy-6-methoxyacetophenone (Baker, *J.*, 1939, 959); 2-hydroxy-6-benzyloxy-, 2 : 6-dihydroxy-, 2-hydroxy-3-methoxy-, and 2-hydroxy-5-methoxy-acetophenone, and 2-hydroxy-3-methoxybenzaldehyde (Baker, Brown, and Scott, *J.*, 1939, 1922); 8-methoxycoumarin (Mauthner, *J. pr. Chem.*, 1939, **152**, 23); 2-hydroxy-3 : 4 : 6-trimethoxyacetophenone (Baker, *J.*, 1941, 669). Of particular interest is the application of the reaction by Seshadri and his co-workers to the flavone and related series, whereby 5-hydroxyflavones and their derivatives were converted into 5 : 8-dihydroxy-derivatives; the reactants were 5-hydroxy-3 : 7-dimethoxy-, 5 : 7-dihydroxy-3-methoxy-, 5-hydroxy-3 : 7 : 3′ : 4′-tetramethoxy-, 5 : 7-dihydroxy-3 : 3′ : 4′-trimethoxy-, 5-hydroxy-, 5-hydroxy-3 : 7 : 4′-trimethoxy-, 5-hydroxy-3 : 7 : 3′ : 4′ : 5′-pentamethoxy-, and 5 : 7-dihydroxy-3 : 3′ : 4′ : 5′-tetramethoxy-flavone and chrysin, chrysin 7-monomethyl ether, and 4-hydroxy-6-methoxyxanthone (*Proc. Indian Acad. Sci.*, 1947, **25***A*, 417, 427, 432, 444; **26***A*, 288).*

General Reaction Conditions.—A study of the oxidation of a number of simple phenols has established the optimum reaction conditions which are described in the experimental section. No significant advantage is gained by the use of ammonium in place of potassium persulphate, or by addition of ferric chloride as recommended by Bargellini. The yield is sometimes improved by carrying out the oxidation in solutions saturated with sodium chloride or sulphate. With phenols difficultly soluble in aqueous alkali owing to co-ordination with an adjacent carbonyl group, Seshadri recommends addition of pyridine. Where the dihydric phenol is easily soluble in water, and is not readily extracted therefrom, it is an advantage to saturate the solution with carbon dioxide after the oxidation, extract it with ether (an alternative, which frequently removes flocculent material, is to acidify to Congo-red, filter, extract with ether, and make alkaline to litmus with sodium hydrogen carbonate), evaporate the aqueous layer to dryness under diminished pressure, dissolve out the phenyl potassium sulphate derivative with 90% alcohol,

* *Note added in Proof.*—Further examples have been described by Seshadri *et al.* in *Proc. Indian Acad. Sci.*, 1946, **23***A*, 23, 262; 1948, **27***A*, 37, 85, 91, 209, 217, 375; 1948, **28***A*, 1.

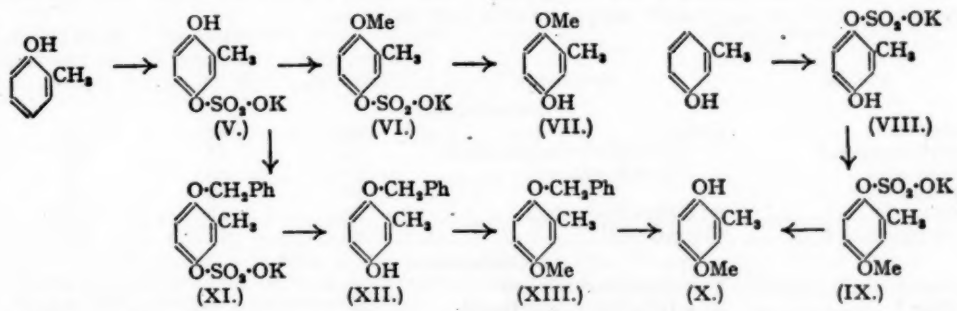
distil off the alcohol, and hydrolyse the residue with a small volume of 2N-acid. The hydrolysis is conveniently effected under a layer of benzene or ether (see Baker, Brown, and Scott, *loc. cit.*).

The Table in the experimental section gives the yields of several dihydric phenols under the standard conditions. In the *p*-oxidations the yields are increased by the presence of electron-attracting groups (this may be due to a general stabilisation of the nucleus), by increasing substitution, and by the effect of substituents on the activity of the position para to the hydroxyl group. The last point is most clearly seen by comparing the yields from the isomeric pair, 2-hydroxy-6-methoxyacetophenone (38%) and 2-hydroxy-3-methoxyacetophenone (4%). The reaction was not successful with α-naphthol.

A side reaction observed during two Elbs persulphate oxidations is an oxidative coupling to give derivatives of diphenyl (Baker, Brown, and Scott, *loc. cit.*); 2-hydroxy-3-methoxybenzaldehyde (*o*-vanillin) gives 2 : 5-dihydroxy-3-methoxybenzaldehyde and a much smaller amount of 4 : 4′-dihydroxy-3 : 3′-dimethoxydiphenyl-5 : 5′-dialdehyde, and 2-hydroxy-5-methoxyacetophenone gives by an ortho-oxidation a very poor yield of 2 : 3-dihydroxy-5-methoxyacetophenone and a much larger amount of 2 : 2′-dihydroxy-5 : 5′-dimethoxy-3 : 3′-diacetyldiphenyl.

The ortho-oxidation of *p*-substituted phenols gives catechol derivatives in very poor yield, and tarry matter is simultaneously produced. The catechols are best isolated and purified by means of their insoluble lead derivatives, which are subsequently decomposed by hydrogen sulphide. No significant yield of catechol derivatives could be obtained from *p-tert.*-butylphenol or β-naphthol.

Preparation of Quinol Monoalkyl Ethers.—The product of interaction of a phenol possessing a free *p*-position and alkaline potassium persulphate is a *p*-hydroxyphenyl potassium sulphate (I), and, owing to the stability of these compounds under alkaline conditions, it is possible to alkylate (I) to (III), and then to hydrolyse (III) in acid solution to the quinol monoalkyl ether (IV), in which the alkyloxy-group occupies the position of the original hydroxyl group. The method, therefore, affords a general process by which quinol monoalkyl ethers of known orientation can be prepared, and the synthetical possibilities are illustrated by the preparation of 5-*benzyloxy*-m-2-*xylenol*, and the two isomeric monomethyl ethers of toluquinol and of 2 : 6-dimethylquinol. *o*-Cresol was oxidised by alkaline potassium persulphate to the intermediate (V), which, after isolation in the crude state, was treated with methyl sulphate in alkaline solution to give (VI), and acid hydrolysis then gave 5-hydroxy-2-methoxytoluene (VII). In a similar manner *m*-cresol gave, *via* the intermediates (VIII) and (IX), 2-hydroxy-5-methoxytoluene (X). By utilising the same series of reactions the two isomeric monomethyl ethers of 2 : 6-dimethylquinol were also obtained, *m*-5-xylenol giving 2 : 6-dimethylquinol 4-methyl ether, and *m*-2-xylenol giving 2 : 6-*dimethylquinol* 1-*methyl ether*.

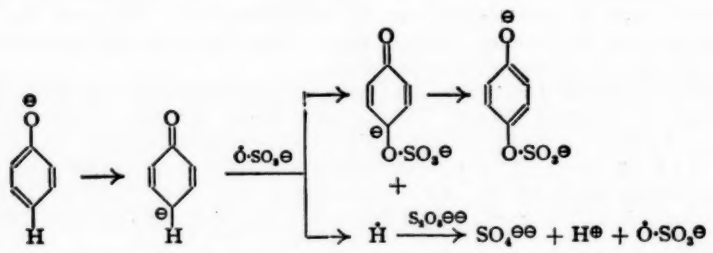


A further synthetical possibility is the preparation of both isomeric monoalkyl ethers of a quinol from the same starting material; this is possible by taking advantage of the fact that a benzyloxy-group is much less readily hydrolysed by acids than is the phenyl sulphate group (see preparation of 2 : 5-dihydroxy-6-benzyloxyacetophenone, Baker, Brown, and Scott, *loc. cit.*). Thus the intermediate (V) from *o*-cresol can be benzylated to (XI), hydrolysed with dilute acid to (XII), methylated to (XIII), and finally hydrolysed in strongly acid solution to (X).

Reaction Mechanism.—The initial and final products of the Elbs persulphate oxidation of phenols are shown in the following ionic equation :

$$\overset{\ominus}{O}\cdot C_6H_5 + S_2O_8^{\ominus\ominus} \longrightarrow \overset{\ominus}{O}\cdot C_6H_4\cdot O\cdot SO_3^{\ominus} + SO_4^{\ominus\ominus} + H^{\oplus}$$

The direct introduction of the group $\cdot O \cdot SO_3^{\ominus}$ in place of a hydrogen atom *p*- or *o*-, but never *m*-, to the phenolic oxygen atom strongly suggests that the reaction is due to the sulphate ion radical $\dot{O} \cdot SO_3^{\ominus}$ which, although an anion, is yet cationoid in character. The reaction is represented in greater detail in the following scheme (only one of the hydrogen atoms of the phenol nucleus is shown) :



The sulphate ion radical is probably first generated by the interaction of a trace of a metal ion, *e.g.*, a ferrous ion, with a persulphate ion :

$$Fe^{\oplus\oplus} + S_2O_8^{\ominus\ominus} \longrightarrow Fe^{\oplus\oplus\oplus} + SO_4^{\ominus\ominus} + O \cdot SO_3^{\ominus}$$

The slow rate of the reaction can be correlated with the requirement that the $\dot{O} \cdot SO_3^{\ominus}$ anion radical has to attack an anion (or neutral molecule if the attack were on the free phenol molecule rather than the phenoxide ion) at a negative centre.

The oxidative coupling of the phenol nuclei which occasionally occurs may be due to the production of hydroxyl radicals by the mechanism $\dot{O} \cdot SO_3^{\ominus} + H_2O \longrightarrow HSO_4^{\ominus} + \dot{O}H$. Substituted phenyl radicals may then be formed, $\overset{\ominus}{O} \cdot C_6H_5 + \dot{O}H \longrightarrow \overset{\ominus}{O} \cdot C_6H_4^{\cdot} + H_2O$, which undergo dimerisation (see Discussion, " Oxidation ", *Trans. Faraday Soc.*, 1946, **42**, 196).

Experimental.

General Reaction Conditions.—The phenolic compound (1 mol.) is dissolved in a 10% solution of sodium hydroxide (5 mols.) and oxidised by the slow addition during 3—4 hours of a saturated aqueous solution of potassium persulphate (1 mol.). Throughout the addition the mixture is continually stirred, and the temperature is not allowed to rise above 20°. After standing overnight, the solution is acidified to Congo-red, filtered if necessary, and extracted twice with ether. The aqueous layer is treated with excess of hydrochloric acid, heated on the water-bath for ½ hour, cooled, and extracted with ether. The extracts are then dried and distilled, yielding the dihydric phenol.

The following Table shows a few new results *, and others † where the yields were previously unrecorded or where an appreciable improvement in yield was made.

Phenol.	Product.	Recovered phenol, %.	Yield of dihydric phenol, %.	Yield allowing for recovered phenol, %.
	p-Oxidations.			
Phenol †	Quinol	48	18	34
Salicylaldehyde †	2 : 5-Dihydroxybenzaldehyde	24	25	33
m-5-Xylenol †	2 : 6-Dimethylquinol	30	36	51
m-2-Xylenol *	,,	26	30	40
p-Xylenol *	2 : 5-Dimethylquinol	25	42	56
o-Chlorophenol *	Chloroquinol	20	50	62
	o-Oxidations.			
p-Cresol †	3 : 4-Dihydroxytoluene	20	9	11
Vanillin *	3 : 4-Dihydroxy-5-methoxybenzaldehyde	48	1·9	3·6
p-Hydroxybenzoic acid †	Protocatechuic acid	71	0·6	2·0

Some of the yields may be raised by isolation of the intermediate phenyl potassium sulphate derivative as previously described, but the process is tedious owing to the evaporation of large volumes of solution.

*5-Benzyloxy-*m*-2-xylenol* (with Dr. R. F. Goldstein).—4-Hydroxy-2 : 6-dimethylphenyl potassium sulphate was prepared from *m*-5-xylenol, and isolated by extraction with 90% alcohol. This salt (25 g.) was boiled and stirred under reflux with 90% alcohol (60 c.c.) and a solution of sodium hydroxide (7 g.) in water (50 c.c.), during addition of benzyl chloride (14 g.) (¼ hour), and then for a further 2 hours. The mixture was now made weakly acid to Congo-red by addition of hydrochloric acid, stirred just below the boiling point for 2 hours, and cooled in ice. The solid *5-benzyloxy-*m*-2-xylenol* (23 g.) crystallises from benzene or light petroleum and has m. p. 97—99° (Found : C, 78·7; H, 6·9. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1%).

5-Hydroxy-2-methoxytoluene (VII).—*o*-Cresol (21 g.) was converted into the intermediate phenyl potassium sulphate (V) (6·5 g. of *o*-cresol were recovered), which was isolated (27 g.) by two extractions with 90% alcohol, and methylated by being shaken in 50% alcohol with a large excess of methyl sulphate and concentrated aqueous sodium hydroxide, the mixture (kept alkaline throughout) being finally heated on the water-bath for ½ hour. The solution was then made strongly acid to Congo-red and heated for ½ hour, and the oily product was extracted with ether and distilled twice, giving a product, b. p. 242—244° (7·3 g.; 27% yield), which solidified, and was then crystallised from benzene–light petroleum; m. p. 46° (Bamberger, *Annalen*, 1912, **390**, 175, records m. p. 46—46·5°).

Preparation of 2-Hydroxy-5-methoxytoluene (X) *from* m-*Cresol*.—(X) was prepared from *m*-cresol (21 g.). *m*-Cresol (6·5 g.) was recovered, and (X) isolated after two distillations, b. p. 240—243° (9·2 g.; 34% yield), and final crystallisation from water. It had m. p. 71° (Bamberger, *loc. cit.*, p. 174, records m. p. 70·5—71·5°).

5-Hydroxy-2-benzyloxytoluene (XII) (With Mr. F. Glockling).—The crude phenyl potassium sulphate derivative (V) was prepared from *o*-cresol, and a portion (20 g.) was benzylated as in the preparation of 5-benzyloxy-*m*-2-xylenol, using 90% alcohol (60 c.c.), sodium hydroxide (6 g.) in water (50 c.c.), and benzyl chloride (15 g.). After hydrolysis of the sulphate group, the product (XII) was extracted with ether, transferred to aqueous sodium hydroxide, reprecipitated, and again isolated with ether, leaving a dark, partly crystalline solid which was used directly for the preparation of (XIII). Pure *5-hydroxy-2-benzyloxytoluene* (XII) was prepared by shaking the solution of the crude material in chloroform with alumina, and crystallising from light petroleum (b. p. 80—100°) (charcoal); colourless needles, m. p. 69—70° (Found: C, 78·2; H, 6·4. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%).

2-Benzyloxy-5-methoxytoluene (XIII) (With Mr. F. Glockling).—(*a*) The crude phenol (XII) (5·8 g.) was methylated with a large excess of methyl sulphate and 50% aqueous sodium hydroxide in acetone, giving finally crude (XIII) (4·1 g.) which was directly hydrolysed to (X) (below). (*b*) A pure specimen of *2-benzyloxy-5-methoxytoluene* (XIII) was prepared from pure 2-hydroxy-5-methoxytoluene (X) by benzylation, giving a colourless oil, which distilled at 135—138°/0·5 mm., and solidified in solid carbon dioxide–acetone (Found: C, 79·3; H, 7·3. $C_{15}H_{16}O_2$ requires C, 79·0; H, 7·1%).

2-Hydroxy-5-methoxytoluene (X) *from* (XIII).—The crude compound (XIII) [(*a*) above] (4·1 g.) was heated with acetic acid (30 c.c.) and concentrated hydrochloric acid (15 c.c.) at 60—70° for 2 hours, poured into water (25 c.c.), and extracted with ether. The ethereal extract was shaken with aqueous sodium hydroxide, the aqueous layer acidified, and the product isolated by means of ether and crystallised twice from light petroleum (b. p. 60—80°) (charcoal), giving 2-hydroxy-5-methoxytoluene (X) (0·77 g.), m. p. and mixed m. p. 71°.

5-Methoxy-m-*2-xylenol from* m-*5-Xylenol*.—The phenyl potassium sulphate intermediate prepared from *m*-5-xylenol was methylated and hydrolysed as in the preparation of (VII). The neutralised reaction mixture was steam-distilled, yielding 5-methoxy-*m*-2-xylenol, m. p. 77° (Bamberger, *Ber.*, 1903, **36**, 2040 records m. p. 77—77·5°).

2-Methoxy-m-*5-xylenol from* m-*2-Xylenol*.—This *compound* was prepared as the preceding isomeride. It separates from water in needles, m. p. 83° (Found: C, 71·2; H, 7·9. $C_9H_{12}O_2$ requires C, 71·1; H, 7·9%).

The authors are indebted to Dr. C. E. H. Bawn and Mr. G. E. Coates for valuable discussions on the reaction mechanism. Their thanks are due to Imperial Chemical Industries Ltd. for permission to record the preparation of 5-benzyloxy-*m*-2-xylenol, which was made in their laboratories at Blackley, and for gifts of specimens of the three isomeric xylenols.

The University, Bristol.
The Dyson Perrins Laboratory, Oxford University. [*Received, March 4th*, 1948.]

---

464. *Further Studies on the Sydnones.*

By Ronald A. Eade and J. Campbell Earl.

Weakly alkaline salts decompose *N*-phenylsydnone giving products different from those obtained with sodium hydroxide. *C*-Bromo-*N*-phenylsydnone on alkaline decomposition gives principally aniline, sodium nitrite, and sodium oxalate. The optical activity of (−)-*N*-nitroso-α-anilinophenylacetic acid disappears during its conversion into *CN*-diphenylsydnone. Several new sydnones have been prepared.

N-Phenylsydnone (I) (Earl and Mackney, *J.*, 1935, 899; Eade and Earl, *J.*, 1946, 591; Earl, *Nature*, 1946, **158**, 909) is completely soluble in boiling water and can be recrystallised from it without decomposition. In the presence of some salts, however, rapid decomposition occurs with evolution of carbon dioxide and deposition of tarry products (*Nature*, 1946, **158**, 909). Among the salts which bring about this decomposition are sodium carbonate, acetate, and oxalate, potassium chromate, and lead acetate. Other salts such as sodium chloride, sulphate, iodate, and thiosulphate have no apparent effect. The obvious conclusion is that salts of weak acids which undergo slight hydrolysis in aqueous solution are those which are effective. In other words, a slight increase in pH causes decomposition of *N*-phenylsydnone in boiling aqueous solution. The decomposition reaction is self-inhibiting. After the first vigorous reaction, evolution of gas

soon ceases and if the resinous product is removed by filtration most of the *N*-phenylsydnone is recovered unchanged. This is easily understandable if acid by-products are formed. By boiling solutions of *N*-phenylsydnone in mixtures of N/20-sodium oxalate and N/20-sodium hydrogen oxalate it has been determined that the critical pH above which decomposition occurs is about 5·0. Under mildly alkaline conditions, therefore, *N*-phenylsydnone gives a product which is readily decarboxylated and forms resins, while under more strongly alkaline conditions *N*-nitrosophenylglycine is formed almost quantitatively (*J.*, 1935, 899). *N*-Phenyl-*C*-methylsydnone is much more stable in aqueous solution and decomposition under the influence of added salts was not observed. Most of the other sydnones hitherto described are too little soluble in water for this type of decomposition to occur.

The bromination of *N*-phenylsydnone was recorded by Kenner and Mackay (*Nature*, 1946, **158**, 909). *C*-Bromo-*N*-phenylsydnone is a white crystalline substance, m. p. 134°, becoming red on prolonged exposure to light. It is easily decomposed by hot aqueous alkalis, giving a strong odour of phenyl *iso*cyanide. A roughly quantitative experiment with boiling 5% sodium hydroxide solution showed the principal products to be aniline (90% of theory), sodium nitrite (60%), and sodium oxalate (45%). Once the aniline had been steam-distilled from the reaction mixture, the latter did not give a red colour on being acidified and added to alkaline β-naphthol, so that sodium benzenediazoate is not a decomposition product as stated by Kenner and Mackay. The sodium oxalate probably results from the oxidation of sodium glyoxylate, first formed.

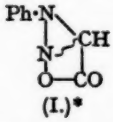
CN-*Diphenylsydnone* has been prepared by a modification of the usual procedure from both racemic and optically active *N*-nitroso-α-anilinophenylacetic acids. The products were identical and inactive showing that the asymmetry of the carbon responsible for the activity disappears during sydnone formation.

Other *sydnones* which have been prepared in addition to those previously described are the *N*-benzyl-, *N-cyclo*hexyl-, *N-m*-bromophenyl-, *N-p*-bromophenyl-, *N-o*-carboxyphenyl-, *N-p*-carboxyphenyl-, *C*-phenyl-*N*-methyl-, and *C*-chloro-*N*-phenyl derivatives.

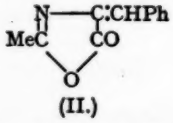
The molecular structure of the sydnones has been the subject of comments by Baker and Ollis (*Nature*, 1946, **158**, 703) and Kenner and Mackay (*ibid.*, p. 909).

It is pointed out that the difficulty in formulating them can be overcome by assuming a single dipolar structure or a hybrid of two or more dipolar structures. The determination of the dipole moments of several members of the series gave a range of values from 6·09 to 6·92 D. (Earl, Leake, and Le Fèvre, *Nature*, 1947, **160**, 366). It is improbable that any single dipolar structure would have a dipole moment as low as this, but the existence of mesomerism would be quite consistent with values of the observed magnitude and range.

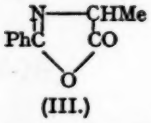
The formation of the sydnones has some counterpart in other dehydration reactions involving the carbonyl instead of the nitroso-group. Erlenmeyer and Früstück (*Annalen*, 1895, **284**, 47) observed such a reaction with a mixture of glycine, benzaldehyde, sodium acetate, and acetic anhydride. The compound formed was eventually assigned the structure (II) (Erlenmeyer,



(I.)*



(II.)



(III.)

ibid., 1904, **337**, 265). Benzoylalanine and other similar compounds were dehydrated to give a series of anhydrides designated lactimones (III) (Mohr and Stroschein, *Ber.*, 1909, **42**, 252; *J. pr. Chem.*, 1910, **81**, 478). In none of these cases, however, is there any difficulty in assigning a classical type of structure.

Experimental.

Decomposition of N-*Phenylsydnone by Boiling Sodium Acetate Solution.*—To a boiling solution of *N*-phenylsydnone (0·200 g.) in water (50 ml.) a 10% solution of crystallised sodium acetate (5 ml.) was added, and the gas evolved passed through calcium chloride into a weighed soda–lime tube. The increases in weight in two experiments were 0·0100 and 0·0112 g., corresponding to 18 and 20% of the amount of carbon dioxide which would be derived from complete decarboxylation. With 10 ml. of sodium acetate solution, the weight of carbon dioxide collected was 0·0130 g. or 24%, but with 20 ml. of the solution no apparent decomposition occurred during 15 mins.' boiling. With the more concentrated solution the critical pH is presumably not reached under the conditions of the experiment.

Determination of Critical pH *for the Decomposition of* N-*Phenylsydnone.*—Powdered *N*-phenylsydnone (1 g.) was added to boiling N/20-sodium oxalate solution (20 ml.). Decomposition with the evolution of gas and deposition of tarry material took place almost immediately. Under similar conditions

* For the meaning of the wavy line see Earl, *Nature*, 1946, **158**, 909.

N/20-sodium hydrogen oxalate caused no decomposition. Experiments with mixtures of the two standard solutions gave the following results:

N/20-$NaHC_2O_4$, ml.	N/20-$Na_2C_2O_4$, ml.	Decomposition observed.	pH of mixed solns. at 15°.*
2	18	None	4·87
1·5	18·5	After 2·5 mins.	4·98
1	19	After 1·25 mins.	5·17
0	20	Immediate	7·30

* Kindly determined by Mr. J. N. Phillips.

Decomposition of C-*Bromo*-N-*phenylsydnone by Sodium Hydroxide.*—*C*-Bromo-*N*-phenylsydnone (1 g.) was mixed with a solution of sodium hydroxide (5 g.) in water (100 ml.) and distilled until the distillate gave no colour with a solution of bleaching powder. The distillate (50 ml.) was made acid with hydrochloric acid and extracted with benzene. After separation, the aqueous layer was cooled and diazotised with a concentrated solution of sodium nitrite (0·4 g.) and was then poured into an alkaline solution of β-naphthol (0·7 g.). The precipitated benzeneazo-β-naphthol was filtered off, washed, and dried in a desiccator at room temperature to constant weight (0·9334 g.; corresponding to 0·346 g. of aniline or 90% of the maximum amount obtainable by quantitative decomposition). The residue in the distillation flask, after cooling, was filtered from a small dark coloured precipitate and made up to 100 ml.; 25 ml. of this solution were made acid with acetic acid and heated nearly to boiling, and excess of calcium chloride solution was added. After standing for some time, the precipitate was filtered off through a weighed Gooch and dried to constant weight at 100° (0·0686 g.). Calculated as $CaC_2O_4.H_2O$, this corresponds to 45% of that obtainable if the two carbons of the sydnone ring were completely converted into oxalic acid. To another 25 ml. of the alkaline solution, aniline (0·2 g.) was added, and the mixture made acid with acetic acid. After standing, the precipitated diazoaminobenzene was filtered off, washed well, and dried to constant weight at room temperature (0·1266 g.), corresponding to 62% of the amount of sodium nitrite theoretically obtainable.

CN-*Diphenylsydnone.*—Powdered α-anilinophenylacetic acid (5 g.) was stirred with a mixture of 100 ml. of glacial acetic acid and 100 ml. of water and cooled to 3—5°. During 10 mins. a solution of sodium nitrite (1·75 g.) in water (5 ml.) was added in small portions, and stirring at 3—5° continued for 90 mins. After removal of a small amount of undissolved material the filtrate was extracted with benzene (80 ml. in 4 portions). The benzene solution was dried (Na_2SO_4), mixed with an equal volume of acetic anhydride, and kept for 23 hours. The solution was shaken well with water, then with dilute sodium carbonate and again with water. On spontaneous evaporation of the dried benzene solution, a dark, partly crystalline *product* was obtained. After being washed with ligroin and recrystallised once from methanol it gave 1·24 g. of pale sandy crystals, m. p. 183—184° (Found: C, 70·2; H, 4·25; N, 11·7. $C_{14}H_{10}O_3N_2$ requires C, 70·6; H, 4·2; N, 11·8%).

Conversion of (−)-α-*Anilinophenylacetic Acid into Sydnone.*—Some (±)-α-anilinophenylacetic acid was resolved by the method of Mackenzie and Bate (*J.*, 1915, **107**, 1683). By carrying out the conversion into sydnone as described above, 1·5 g. of (−)-acid ($[\alpha]_D^{20°}$ in alcohol, − 110°) gave 0·64 g. of optically inactive sydnone, m. p. 184—185°. In another experiment, 0·233 g. of the (−)-acid was nitrosated in the usual way and the rotation of the dried benzene solution observed. It remained constant at − 0·62° during 2 hours. Some of the benzene solution was then mixed with half its volume of acetic anhydride and the change in rotation observed:

Time, mins.	4	8	17	36	65	83	1080
$\alpha_D^{20°}$	−0·52°	0·44°	0·38°	0·31°	0·16°	0·11°	0·0°

N-*Benzylsydnone.*—Benzylglycine ethyl ester (98 g.), prepared by the method of Mason and Winder (*J.*, 1894, **65**, 188), was hydrolysed by boiling with a solution of sodium hydroxide (40 g.) in water (250 ml.) for ½ hour. After extraction with ether and removal of residual ether by boiling, the alkaline solution was neutralised to Congo-red with hydrochloric acid and nitrosated at 0° by adding a solution of sodium nitrite (34·5 g.) in water (100 ml.) during ½ hour. After a further 2 hours' stirring at 0°, the clear solution was acidified, whereupon the *nitroso*-compound separated as a colourless viscous oil which solidified after keeping in the refrigerator; yield, 58·0 g.; m. p. 128—130° (decomp.). Purification was effected by dissolving in 2N-ammonia, filtering, precipitating with acid, and subsequently recrystallising from hot water; 40·1 g.; m. p. 140—140·5°, raised by further recrystallisation to 140·5—141° (Found: C, 55·4; H, 5·2; N, 14·5. $C_9H_{10}O_3N_2$ requires C, 55·65; H, 5·2; N, 14·4%). The nitroso-compound (19·4 g.) was dissolved in acetic anhydride (90 ml.) and kept at 75—80° for 6 hours. The mixture was poured into water, and the product filtered off and washed; 14·7 g. (83%); m. p. 67—68°. Recrystallisation from aqueous alcohol raised the m. p. of the *sydnone* to 68—69° (Found: C, 61·5; H, 4·6; N, 16·0. $C_9H_8O_3N_2$ requires C, 61·4; H, 4·6; N, 15·9%).

N-cyclo*Hexylsydnone* (with S. KRUGER).—*N-cyclo*Hexylglycine hydrochloride (6·3 g.) was dissolved in water, and a solution of the calculated quantity of sodium nitrite added at 0—5°. The nitroso-compound which separated was recrystallised from hot water; 4·1 g. (55%); m. p. 112—114° (decomp.). The pure compound has m. p. 117—118° (decomp.) (Zelinsky and Arzybaschew, *Ber.*, 1907, **40**, 3055). The nitroso-compound (3·7 g.) was mixed with acetic anhydride and kept in the dark at room temperature for 24 hours. Water (100 ml.) was then added, and the mixture shaken for 90 mins. To the clear solution ammonia was cautiously added, with cooling, until it was faintly alkaline. A white oil separated and soon solidified; 1·75 g. (52%), m. p. 48—51°, raised by repeated recrystallisation from hot water to 64·5° (Found: N, 16·3. $C_9H_{12}O_3N_2$ requires N, 16·6%).

N-m-*Bromophenylsydnone.*—m-*Bromophenylglycine ester* was prepared by heating an alcoholic solution (25 ml.) of equimolecular proportions (0·2 g.-mol.) of *m*-bromoaniline, ethyl bromoacetate, and crystalline sodium acetate in an oil-bath at 120° under reflux for 4 hours. The crude ester (49·7 g.; m. p. 104—108°), precipitated on pouring the reaction mixture into water, was recrystallised from

alcohol, 37·5 g., m. p. 118·5—119°, being obtained (Found: C, 46·45; H, 4·7; N, 5·5. $C_{10}H_{12}O_3NBr$ requires C, 46·6; H, 4·7; N, 5·4%). Hydrolysis of the ester was carried out in the usual way, affording an almost quantitative yield of the *glycine*, m. p. 102·5—103·5° (Found: C, 41·5; H, 3·5; N, 6·1. $C_8H_8O_2NBr$ requires C, 41·7; H, 3·5; N, 6·1%). Nitrosation of the glycine (25·5 g.) suspended in water (100 ml.) at 0—5° with a slight excess of sodium nitrite, followed after 3½ hours by acidification, gave the crude *nitroso*-compound [27·0 g., m. p. 116·5—117·5° (decomp.)]. Recrystallisation from aqueous alcohol raised the m. p. to 119—120° (decomp.) (Found: C, 36·4; H, 2·7; N, 10·9. $C_8H_7O_3N_2Br$ requires C, 37·1; H, 2·7; N, 10·8%). The nitroso-compound (13·0 g.) was mixed with acetic anhydride (45 ml.) and kept at room temperature for 6 days. Part of the *sydnone* was filtered off directly from the reaction mixture, and part was recovered from the filtrate on mixing with water. A combined yield of 9·0 g. (75%), m. p. 151—152° (decomp.), was obtained. Recrystallisation from alcohol raised the m. p. to 152—153° (decomp.) (Found: C, 39·4; H, 2·0; N, 11·6. $C_8H_5O_3N_2Br$ requires C, 39·9; H, 2·1; N, 11·6%).

N-p-*Bromophenylsydnone*.—*p*-Bromophenylglycine has been described by Dennstedt (*Ber.*, 1880, **13**, 238) and by Schwalbe, Schulz, and Jochheim (*Ber.*, 1908, **41**, 3795). Our preparation (m. p. 150°) was identical with that of the latter authors and differed from Dennstedt's (m. p. 98°). It was nitrosated similarly to the *m*-bromo-compound, except that the glycine (57·5 g.) was suspended in a mixture of alcohol (50 ml.) and water (200 ml.). The yield of crude product was 62·0 g. (95%), m. p. 126° (decomp.). Recrystallisation from aqueous alcohol raised the m. p. only slightly (Found: C, 36·8; H, 2·8; N, 10·8. $C_8H_7O_3N_2Br$ requires C, 37·1; H, 2·7; N, 10·8%). The *nitroso*-compound (52·0 g.) was dissolved in acetic anhydride (180 ml.), the solution being filtered after 1 day and then kept at room temperature for 13 days. The white crystalline precipitate which had separated was then triturated with dilute alcohol and dried in a vacuum; 15·3 g., m. p. 137·5—138·5° (decomp.). A further 17·0 g. of less pure product, m. p. 130—132° (decomp.), was recovered by decomposing the acetic anhydride in the mother-liquor. On attempting to recrystallise the well-crystallised *sydnone* of m. p. 137·5—138·5° it decomposed. It was, therefore, analysed without further treatment (Found: C, 39·7; H, 2·1; N, 11·7%).

N-o-*Carboxyphenylsydnone*.—*o*-Carboxyphenylglycine (39 g.) was dissolved in a hot solution of sodium hydroxide (8 g.) in water (300 ml.). On cooling quickly to 0—5°, the sodium salt separated. To the suspension, sodium nitrite (15 g.) in water (50 ml.) was added with stirring during 30 mins. After another 3½ hours' stirring at 5° a clear solution was obtained, from which on acidification, the nitroso-compound separated slowly as a cream powder; 35·1 g., m. p. 112—113° (decomp.). It was readily soluble in warm water and recrystallised on cooling without change of m. p. Van Ekenstein and Blanksma (*Rec. Trav. chim.*, 1905, **24**, 36) record m.p. 120° (decomp.) (Found: equiv., 114·2. Calc. for $C_9H_8O_5N_2$: equiv., 112·1). The nitroso-compound (22·4 g.) was dissolved in acetic anhydride (90 ml.) and kept for 3 weeks. The crude *product* obtained after decomposing the acetic anhydride was recrystallised once from alcohol (charcoal); yield, 9·7 g., m. p. 204—205° (decomp.), raised by recrystallisation to 205—206° (Found: C, 51·9; H, 2·9; N, 13·0. $C_9H_8O_4N_2$ requires C, 52·4; H, 2·9; N, 13·6%). On account of rapid decomposition during combustion, it was difficult to obtain consistent analytical figures.

N-p-*Carboxyphenylsydnone*.—The following procedure gave purer *p*-carboxyphenylglycine than that obtained by Mauthner and Suida (*Monatsh.*, 1890, **11**, 380). Sodium hydrogen carbonate (33·6 g.) was added to a mixture of bromoacetic acid (27·8 g.), *p*-aminobenzoic acid (27·2 g.), and water (250 ml.), and the solution boiled under reflux for 4 hours. On cooling, the monosodium salt of *p*-carboxyphenylglycine separated and was filtered off. It was dissolved in sodium hydroxide solution, and the crude glycine [26·1 g.; m. p. 241—243° (decomp.)] precipitated by acidification to pH 1—2. On digestion with hot glacial acetic acid (400 ml.), part of the glycine [11·1 g.; m. p. 255° (decomp.)] remained undissolved, and more [7·0 g.; m. p. 255° (decomp.)] was recovered on cooling the acetic acid solution; total yield, 18·1 g. (46%). The nitroso-derivative was prepared similarly to that of the *o*-carboxy-compound, rather more water (525 ml.) and a longer reaction time (9 hours) being required. Conversion into the *sydnone* was brought about by heating the nitroso-compound (22·4 g.) with acetic anhydride (90 ml.) at 80°. After isolation in the usual way, 14·4 g.(70%) of crude product, m. p. 242—243° (decomp.), were obtained. Recrystallisation from *cyclo*hexanone raised the m. p. to 248—249° (decomp.) (Found: C, 52·2; H, 2·9; N, 13·5%).

C-*Phenyl*-N-*methylsydnone*.—Phenylsarcosine (1·91 g.) was dissolved in a mixture of glacial acetic acid (20 ml.) and water (20 ml.) and cooled to 2°; a solution of sodium nitrite (0·82 g.) in water (10 ml.) was added, and the mixture kept at 0—5° for 70 mins. It was then extracted rapidly with two successive mixtures of benzene (15 ml.) and acetic anhydride (10 ml.), the extract being allowed to stand in the dark for three days. It was then shaken well with water, and the benzene layer separated and dried (Na_2SO_4). On evaporation, first on the water-bath and later at room temperature, a semicrystalline residue was obtained which was washed thoroughly with cold water and dried in a desiccator; 0·42 g., m. p. 115—120°. One recrystallisation from hot water gave 0·22 g. of pure white crystalline *sydnone*, m. p. 131—132° (Found: C, 60·8; H, 4·5; N, 15·65. $C_9H_8O_2N_2$ requires C, 61·3; H, 4·6; N, 15·9%).

C-*Chloro*-N-*phenylsydnone*.—*N*-Phenylsydnone (1 g.) and crystalline sodium acetate (1 g.) were dissolved in glacial acetic acid (20 ml.), and chlorine bubbled in until no more was absorbed (0·5 g.). The solution was mixed with water, and the precipitated *product* filtered off, recrystallised from aqueous alcohol, and dried in air; 0·45 g., m. p. 127° (decomp.) (Found: Cl, 17·8; N, 13·8. $C_8H_5O_2N_2Cl$ requires Cl, 18·0; N, 14·25%).

The authors thank Miss J. Fildes for the many microanalyses done in connexion with this work.

UNIVERSITY OF SYDNEY AND
SYDNEY TECHNICAL COLLEGE, N.S.W.

[*Received, September 29th*, 1947.]

465. *Pectic Substances. Part VIII. The Araban Component of Sugar-beet Pectin.*

By E. L. Hirst and J. K. N. Jones.

Methylation of crude pectic material isolated from sugar beet gave a product from which could be separated material which closely resembled the methylated araban obtained from other plant pectins. On methanolysis, this methylated araban yielded in approximately equimolecular proportions 2 : 3 : 5-trimethyl methyl-L-arabinoside, 2 : 3-dimethyl methyl-L-arabinoside, and 2-methyl methyl-L-arabinoside. The ease of hydrolysis indicates that the polysaccharide is built up of L-arabofuranose residues and it appears to be identical in structure with the araban present in the peanut (Hirst and Jones, *J.*, 1947, 1221).

The presence in sugar beet of a polysaccharide containing L-arabinose residues was suggested some 75 years ago by Scheibler (*Ber.*, 1873, **6**, 612), who found that extraction of the beet with lime water yielded a solution of a gum which, on acidic hydrolysis, gave a good yield of L-arabinose. Later work by Ehrlich and Schubert (*Ber.*, 1929, **62**, 1974) confirmed this observation. Ehrlich considered that the araban was of comparatively low molecular weight, and Gaponenkov (*J. Gen. Chem. Russia*, 1937, **7**, 1729) reported that the polysaccharide had a molecular weight of the order of 6000. It was not, however, until 1945 that Ingelman (*Communications Swedish Sugar Corp.*, 1945, **1**, 179) detailed the actual isolation of the araban from sugar beet and described its physical properties. The optical rotation ($[\alpha]_D$ *ca.* $-130°$) suggested that this araban was closely similar to, if not identical with, the araban present in pectic materials isolated from other plant sources.

In the present experiments, attempts were made first of all to extract the araban by the methods detailed by earlier workers (Scheibler, *loc. cit.*), but difficulty was experienced in obtaining it in a sufficiently high degree of purity when fresh beet, or sugar beet chips from which the sucrose had been removed by extraction, were used as source. Earlier work on the pectic components of the peanut (Hirst and Jones, *J.*, 1938, 496; 1939, 452) had shown that, under the usual conditions of methylation with sodium hydroxide and methyl sulphate, the pectic acid component is largely destroyed, and that the araban component is converted into an insoluble methyl ether derivative much more rapidly than is the galactan component. Application of this methylation procedure to a sample of crude araban which had been isolated by extraction of sugar beet chips with lime water according to the method of Scheibler (*loc. cit.*) led to the isolation of a methylated araban. This material had $[\alpha]_D$ *ca.* $-150°$ in acetone, compared with *ca.* $-170°$ for the purest sample of methyl araban isolated from peanut araban, but somewhat lower figures have been obtained for other samples of methylated peanut araban and for methylated apple araban (Hirst and Jones, *J.*, 1939, 454). The presence of a small amount of contaminant was shown in that after methanolysis of the methylated beet araban there remained a small quantity of a difficultly hydrolysable residue, and it is probable that the difference in optical rotation of the samples of methylated araban is due to the presence of this impurity. It is clear that traces of methylated galactan or pectic acid, with their high positive rotations, would account for the variations.

Methanolysis of the methylated araban, followed by fractional distillation of the products, gave three fractions in approximately equimolecular proportions. These were (*a*) 2 : 3 : 5-trimethyl methyl-L-arabofuranoside, which was further characterised as the crystalline lactone and the crystalline amide of 2 : 3 : 5-trimethyl L-arabonic acid (Baker and Haworth, *J.*, 1925, 365); (*b*) 2 : 3-dimethyl methyl-L-arabinoside, identified as the crystalline anilide of 2 : 3-dimethyl L-arabinose and as the crystalline amide of 2 : 3-dimethyl L-arabonic acid (Smith, *J.*, 1939, 753); and (*c*) 2-methyl methyl-L-arabinoside characterised as the crystalline phenylhydrazone of 2-methyl L-arabinose and as the crystalline amide of 2-methyl L-arabonic acid (Hirst and Jones, *J.*, 1947, 1221). Confirmation of the presence of three methylated derivatives of arabinose was obtained from a study of the reducing sugars produced on hydrolysis of methylated araban. A solution of the sugar derivatives on examination on the paper chromatogram showed three widely separated spots of approximately equal intensity. The isolation of these three derivatives of L-arabinose in approximately equimolecular proportions shows that the araban possesses a branched chain structure. The isolation of the 2 : 3 : 5-trimethyl methyl-L-arabinoside proves that at least one-third of the pentose residues is in the furanose form. The high negative rotation of the methylated araban, coupled with its ease of methanolysis, indicates that in all probability all the L-arabinose residues are present as furanosides in the polysaccharide. The position reached in the delineation of the possible

structures which satisfy the experimental observations is exactly the same as in the case of peanut araban discussed earlier (Hirst and Jones, *loc. cit.*). It is clear that one-third of the arabinose residues are attached in the form A,1 . . . and therefore are end groups. Another set of arabinose residues is present in the form . . . 5A,1 . . ., linked through positions 1 and 5, and the remaining arabinose residues occur as $\begin{matrix}\cdot\cdot\cdot\\ \cdot\cdot\cdot\end{matrix}\!\!>\!\!\begin{matrix}3\\5\end{matrix}$A,1 . . . ., linked through positions 1 and 3. It is clear also that sugar-beet pectin resembles the other pectins we have examined, derived from citrus fruit, peanut, and apple, in that it contains a polymer built up of L-arabofuranose residues which cannot arise by direct decarboxylation of the uronic acid residues in the pectic acid, which is intimately associated with the araban.

Experimental.

(All b. p.s recorded in distillations are bath temperatures.)

Sugar-beet chips, which had previously been extracted with water to remove sucrose, were used as the source of araban. The extracted material (500 g.) was mixed with water (4 l.) containing calcium hydroxide (100 g.) and the whole heated on the steam-bath for 12 hours. The slurry was filtered through cloth and the filtrate was centrifuged. The clear solution was then acidified with acetic acid, and the solution filtered to remove degraded pectic acid. On addition of alcohol, crude araban, contaminated with calcium acetate, was precipitated. The product was purified by dissolving it in water (250 c.c.); the insoluble material was filtered off, and the araban reprecipitated by the addition of alcohol. This crude product (*ca.* 5 g.) was used in subsequent experiments.

Acetylation.—The crude araban (1 g.) was suspended in pyridine (50 c.c.), and acetic anhydride (15 c.c.) added. The mixture was heated on the steam-bath for 6 hours, cooled, and the insoluble material removed on the centrifuge. Crude araban acetate was precipitated on pouring the pyridine solution into water. It was filtered off, washed with water, and purified by reprecipitation from acetone solution by the addition of water. The product (0·4 g.) had $[\alpha]_D^{20°}$ − 84° (*c*, 0·36 in acetone) (Found: OAc, 39. Calc. for a diacetyl araban: OAc, 37·2%). On deacetylation by the method of Zemplén and Kunz (*Ber.*, 1923, **56**, 1705), an araban (0·1 g.), $[\alpha]_D^{20°}$ − 114° (*c*, 0·4 in water), was isolated. Ingelman reports $[\alpha]_D$ − 129° for an araban isolated from sugar beet.

Methylation.—The crude araban (10 g.) was methylated with sodium hydroxide and methyl sulphate, and the crude product (6 g.) purified, after 6 methylations, by solution in acetone followed by filtration. Methylation of the acetone-soluble fraction was completed by boiling it with silver oxide and methyl iodide. The product (5·2 g.; OMe, 36·7%) was fractionated by addition of light petroleum (b. p. 40—60°) to its acetone solution. Fraction (I) was a yellow solid (2·4 g.), $[\alpha]_D^{20°}$ −148° (*c*, 1·3 in acetone) (Found: OMe, 36·2. Calc. for dimethyl araban: OMe, 38·8%). Fraction (II) was a yellow solid (1·5 g.), $[\alpha]_D^{20°}$ −146° (*c*, 0·55 in acetone) (Found: OMe, 36·8%). Fraction (III) (1·3 g.) was a sticky yellow solid which was not further examined.

Hydrolysis.—(a) *Qualitative.* Methylated araban [Fraction (I)] (12 mg.) was dissolved in methyl alcohol (1 c.c.) and 3N-hydrochloric acid (0·5 c.c.) added. The solution was heated at 70° for 12 hours. The temperature was then raised to 90° and the solution concentrated to *ca.* 0·2 c.c. A spot of the solution was withdrawn, mixed with one spot of ammonia (*d* 0·88), and the mixture of sugars separated on a paper chromatogram by the method of Partridge (*Nature*, 1946, **158**, 270), as used by Flood, Hirst, and Jones for methylated sugars (*ibid.*, 1947, **160**, 86) with a mixture of butanol (50%), ethanol (10%), and water (40%) for development. After 20 hours the paper was removed from the apparatus, dried in a steam-oven, and sprayed with ammoniacal silver nitrate. After removal of the solvent in the steam-oven, the position of the reducing sugars was indicated by the formation of a brown stain of silver. Three well separated spots of approximately equal intensity were produced, the presence of three different reducing sugars being thus indicated.

(b) *Quantitative.* Fraction (I) (2·18 g.) was boiled with methanolic hydrogen chloride (100 c.c.; 1% w/v) for 12 hours. It was not possible to follow the change in optical rotation, owing to darkening of the solution. The cooled solution was neutralised with silver carbonate and filtered, and the filtrate concentrated to a syrup (2·39 g.). This syrup was submitted to fractional extraction from aqueous solution in an all-glass continuous extraction apparatus (Brown and Jones, *J.*, 1947, 1344) with light petroleum (b. p. 39—40°) and then with ether, yielding (*a*) a portion soluble in light petroleum (1·38 g.), and (*b*) a portion soluble in ether (0·40 g.). The residue (0·4 g.) in the water was obtained on concentration of the aqueous solution. Portion (*a*) was distilled in a vacuum, giving Fraction (*A*) (0·52 g.), b. p. 90°/0·1 mm., $n_D^{20°}$ 1·4365 (Found: OMe, 59·4%). Portion (*b*) was added to the still residue and the distillation continued, giving Fraction (*B*) (0·67 g.), b. p. 120—130°/0·1 mm., $n_D^{20°}$ 1·4478 (Found: OMe, 49·7%). The water-soluble residue was added to the still residue and the distillation continued, giving Fraction (*C*) (0·46 g.), b. p. 130—140°/0·1 mm., $n_D^{20°}$ 1·4629 (Found: OMe, 38·4%), and Fraction (*D*) (0·31 g.), b. p. 140—160°/0·1 mm., $n_D^{20°}$ 1·4743 (Found: OMe, 34·0%). The still residue (0·28 g.) was not further examined.

Examination of the fractions. Fraction (*A*) (0·52 g.) was hydrolysed with boiling N-sulphuric acid; $[\alpha]_D^{20°}$ changed from −57° to −17° (6 hours; constant value). The syrupy sugar (0·45 g.), $n_D^{20°}$ 1·4568, was isolated by continuous extraction of the neutralised solution with chloroform (Found: OMe, 45·8%). On oxidation with bromine water this fraction gave in good yield crystalline 2 : 3 : 5-trimethyl L-arabonolactone, m. p. and mixed m. p. with an authentic sample, 29°. On reaction with liquid ammonia, the lactone was converted into 2 : 3 : 5-trimethyl L-arabonamide, m. p. and mixed m. p. with an authentic sample, 139°. The figures for the methoxyl content and the optical rotation show that this fraction could contain some 15% of 2 : 3-dimethyl L-arabinose.

Fraction (*B*) (0·67 g.) was boiled (6 hours) with N-sulphuric acid until the optical rotation had become constant; $[\alpha]_D^{20°}$ −48° ⟶ +76°. The reducing sugar (0·59 g.), $[\alpha]_D$ +82° in water, was isolated in the

usual manner (Found: OMe, 36·7%). On boiling a portion of the syrup with alcoholic aniline, 2 : 3-dimethyl L-arabinose anilide was produced, m. p. and mixed m. p., with an authentic sample, 138°. On oxidation with bromine water the sugar gave 2 : 3-dimethyl L-arabonolactone characterised as its crystalline amide, m. p. and mixed m. p. with an authentic sample, 162°. From the optical rotation and methoxyl content, it may be calculated that this fraction contains some 16% of 2 : 3 : 5-dimethyl L-arabinose.

Fraction (*C*) (0·45 g.) was hydrolysed with boiling N-sulphuric acid; $[\alpha]_D$ +5° ⟶ +8·4, yielding a syrup (0·4 g.), $[\alpha]_D^{20°}$ +90°, $n_D^{22°}$ 1·4702 (Found: OMe, 23·6%), which was a mixture of 2 : 3-dimethyl L-arabinose (25%) and 2-methyl L-arabinose (75%). On oxidation with bromine water, it yielded a lactone which partly crystallised after distillation and on nucleation with 2 : 3-dimethyl L-arabonolactone. The crystals were separated on a porous plate and were purified by recrystallisation from ether–light petroleum. They then had m. p. 34°, not depressed on admixture with an authentic sample.

Fraction (*D*) (0·31 g.), on hydrolysis with N-sulphuric acid, yielded a syrup (0·22 g.), $[\alpha]_D$ +100° (Found: OMe, 19·6%); this, on being heated with alcoholic phenylhydrazine, yielded 2-methyl L-arabinose phenylhydrazone, m. p. 116°, not depressed on admixture with an authentic specimen. The methoxyl content indicated that this fraction is a pure monomethyl pentose.

	Wt. of L-arabinose derivatives (g.) calcd. as		
Fraction.	2 : 3 : 5-Trimethyl methyl-L-arabinoside.	2 : 3-Dimethyl methyl-L-arabinoside.	2-Methyl methyl-L-arabinoside.
(*A*)	0·465	0·055	—
(*B*)	0·107	0·563	—
(*C*)	—	0·065	0·385
(*D*)	—	—	0·310
Total	0·572	0·683	0·695
Ratio in g.-mols.	0·8	1·0	1·1

The quantitative data relating to the hydrolysis products obtained from Fraction (I) of the methylated araban are collected together in the Table, which shows the amounts of 2 : 3 : 5-trimethyl methylarabinoside, 2 : 3-dimethyl methylarabinoside and 2-methyl methylarabinoside contained in the Fractions (*A*), (*B*), (*C*), and (*D*). The three sugars are present in the mixture of hydrolysis products in approximately equimolecular proportions.

Fraction (II) (1·44 g.) was hydrolysed by boiling it with methanolic hydrogen chloride (50 c.c., 4%) for 20 hours; ($[\alpha]_D^{20°}$ −20°, constant value). The cooled solution was treated with diazomethane and concentrated to a syrup under reduced pressure. The residual yellow syrup (1·6 g.) was then dissolved in water, and some insoluble brown material was filtered off. The filtrate was made up to 50 c.c. with water and extracted with light petroleum (b. p. 40—60°) in a double extractor of the type described by Brown and Jones (*loc. cit.*). Very little methylated sugar was being removed from the aqueous solution after extraction for 24 hours, and at this stage the light petroleum solution was evaporated to a syrup (*X*, 0·63 g., $n_D^{20°}$ 1·4360) and extraction of the aqueous solution was continued with ether. 24 Hours' extraction sufficed to remove all the ether-soluble material (*Y*, 0·41 g.). Concentration of the residual aqueous solution left a syrup (*Z*, 0·51 g.).

These fractions were further purified by distillation in a vacuum. Fraction (*X*) was distilled, yielding fraction (*E*) (0·48 g.), $n_D^{20°}$ 1·4358, b. p. 100°/0·1 mm. (Found: OMe, 60%). Fraction (*Y*) was then added, and the distillation continued, yielding fraction (*F*) (0·51 g.), b. p. 130°/0·1 mm., $n_D^{20°}$ 1·4568 (Found: OMe, 49·2%). The still residue (80 mg.) was added to the syrup obtained on concentration of the residual aqueous solution and purified by distillation, giving fraction (*G*) (0·47 g.), b. p. 170°/0·1 mm., $n_D^{20°}$ 1·4738 (Found: OMe, 35·2%). The still residue (0·11 g.) was not further examined.

When Fraction (*E*) (0·47 g.) was hydrolysed with N-sulphuric acid, $[\alpha]_D$ changed from −83° to −40° (constant value). The syrupy sugar (0·4 g.), isolated in the usual manner, was oxidised with bromine water, and the resultant 2 : 3 : 5-trimethyl L-arabonolactone, m. p. 30° $[\alpha]_D$ −46° (*c*, 1·31 in water; initial value), was isolated in the manner already described (yield, 0·41 g.) (Found: OMe, 48·7; equiv., 188. Calc. for $C_9H_{14}O_5$: OMe, 48·9%; equiv., 190).

Fraction (*F*) (0·5 g.) was hydrolysed by boiling with N-sulphuric acid; $[\alpha]_D$ −17° (initial value) rising to +90° (constant value). A sample (0·1 g.) of the sugar (0·44 g., $[\alpha]_D$ +96°) gave, on boiling with alcoholic aniline, 2 : 3-dimethyl L-arabinose anilide. m. p. 138°, not depressed on admixture with an authentic specimen. The sugar (0·2 g.), on oxidation with bromine water, was converted into 2 : 3-dimethyl L-arabonolactone, ($[\alpha]_D$ −38°, falling to −27°; *c*, 1·1 in water), characterised as the crystalline 2 : 3-dimethyl L-arabonamide, m. p. and mixed m. p. with an authentic sample, 162°.

Fraction (*G*) (0·4 g., $[\alpha]_D$ −10° in water) was hydrolysed with boiling N-sulphuric acid until the rotation remained constant ($[\alpha]_D$ +94° after 6 hours). The sugar thereby obtained (0·2 g.) (Found: OMe, 19·1%) gave, with alcoholic phenylhydrazine, a poor yield of 2-methyl L-arabinose phenylhydrazone, m. p. and mixed m. p. with an authentic sample, 114°. No crystalline anilide could be obtained. Oxidation of a sample of the sugar (0·1 g.) with bromine water gave a lactone, $[\alpha]_D$ −44° ⟶ −40° (48 hours) (Found: OMe, 19; equiv., 164. Calc. for $C_6H_{10}O_5$: OMe, 19·1%; equiv., 162). The lactone with alcoholic ammonia gave in small yield 2-methyl L-arabonamide, m. p. 131°, $[\alpha]_D$ +52° (*c*, 0·7 in water) (Found: OMe, 17·1%).

Examination of the constants of fractions (*E*), (*F*), and (*G*) indicate that methylated polysaccharide [Fraction (II)] yields 2 : 3 : 5-trimethyl methyl-L-arabinoside (0·51 g.), 2 : 3-dimethyl methyl-L-arabinoside (0·48 g.), and 2-methyl methyl-L-arabinoside (0·47 g.) in approximately equimolecular proportions.

The authors wish to thank Dr. A. Carruthers and the Sugar Beet Corporation for gifts of material.

THE UNIVERSITIES OF BRISTOL, EDINBURGH, AND MANCHESTER. [*Received, March 1st*, 1948.]

466. 2-*Amino*-1 : 3 : 4-*indotriazine. The Reaction between Isatin and Aminoguanidine.*

By Harold King and Jean Wright.

The aim of the investigation was the introduction of basic side-chains into 3-amino-1 : 2 : 4-indotriazine (I) (Rajagopalan, *Proc. Indian Acad. Sci.*, 1943, **18** *A*, 100) with a view to the production of potential antimalarials.

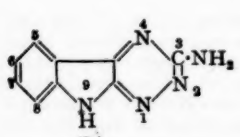
The product of Rajagopalan's reaction was not this indotriazine but *isatin* syn-β-*guanylhydrazone* (II) which could be cyclised in boiling aqueous solution to 2-*amino*-1 : 3 : 4-*indotriazine* (IV). An analogous compound was obtained from *N*-methylisatin. Attempts to attach side-chains to these substances were not successful.

Both parent *syn*-guanylhydrazones were converted in hot alkaline solution into *anti*-guanylhydrazones which could be cyclised to the above 2-aminoindotriazines by sublimation in a high vacuum at 250°. Hot acid treatment converted *isatin* anti-β-*guanylhydrazone* into the *syn*-form.

Diacetylisatin anti-β-*guanylhydrazone* on acid hydrolysis gave di-isatin azine (VI) whereas *acetyl*-*N*-*methylisatin* anti-β-*guanylhydrazone* gave *NN'*-dimethyl*iso*indigotin. These two symmetrical products with alcoholic phenylhydrazine yielded the phenylhydrazones of isatin and *N*-methylisatin respectively.

The *syn*- and *anti*-guanylhydrazones recorded in this communication appear to be the first examples of Hantzsch–Werner stereoisomerism in this type of compound.

By the action of aminoguanidine on isatin in boiling glacial acetic acid solution Rajagopalan (*loc. cit.*) described the formation of a substance to which the constitution of a 3-aminoindotriazine (I) was attributed. As this seemed to be a readily accessible substance it occurred to us that it might be used as a basis for the synthesis of a series of potential antimalarials by the introduction of appropriate basic side-chains.



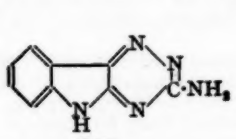
(I.) (II.) (III.)

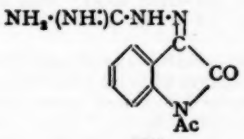
On repetition, however, of Rajagopalan's preparation, a base was obtained to which the constitution of *isatin* syn-β-*guanylhydrazone* (II) is assigned. This base formed a characteristic *hydrochloride* and *nitrate* and when the hydrochloride was digested at 80° with excess of 0·5N-aqueous sodium hydroxide it was converted into an isomeric base to which the constitution *isatin* anti-β-*guanylhydrazone* (III) is attributed. Unlike the *syn*-base this base was a markedly crystalline substance and it formed a characteristic *hydrochloride* and *nitrate* different from the corresponding salts of the *syn*-base. When the hydrochloride of the *anti*-base was boiled in 16% aqueous hydrochloric acid solution the hydrochloride of the *syn*-base separated out. The base Rajagopalan had in hand was undoubtedly the crude *syn*-base and not the tricyclic structure claimed. The 3-aminoindotriazine formula, involving an attack by the ketone reagent on the α-position, which Rajagopalan assigned to his base is contrary to experience and it further involved the loss of a molecule of water, such as is not found to occur. The same doubt applies to the series of substituted 3-aminoindotriazines which De and Dutta (*Ber.*, 1931, **64**, 2605) claimed to have obtained by the action of aminoguanidine on substituted isatins in boiling glacial acetic acid solution.

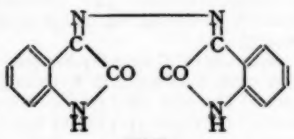
When, however, isatin *syn*-β-guanylhydrazone hydrochloride was boiled in dilute aqueous solution with excess of ammonia for several hours, it was converted with loss of water into a base $C_9H_7N_5$ to which the constitution 2-*amino*-1 : 3 : 4-*indotriazine* (IV) is assigned. Unlike the guanylhydrazones which are all yellow this base is almost colourless and the salts with mineral acids are pale yellow. Under similar conditions isatin *anti*-β-guanylhydrazone does not give this cyclic base but if it is heated to 250° in a high vacuum in a sublimation apparatus it slowly yields the aminoindotriazine as a crystalline sublimate. Attempts to condense this triazine with vinyl cyanide, with ethylene chloro- or bromo-hydrin or with dicyandiamide under a variety of conditions were unsuccessful.

When isatin *anti*-β-guanylhydrazone was boiled with acetic anhydride and pyridine it yielded *mono*- and *di*-*acetylisatin* anti-β-*guanylhydrazones*. The monoacetyl derivative is given the structure (V) since it is soluble in acid solution. When the diacetyl derivative was refluxed with 16% hydrochloric acid a very sparingly soluble maroon-coloured crystalline precipitate separated

which has been identified as di-isatin azine (VI). The acetyl groups play some specific function in the process since, as already mentioned, the parent isatin *anti*-β-guanylhydrazone on boiling with 16% hydrochloric acid gave the *syn*-hydrochloride exclusively.


(IV.)

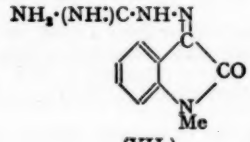

(V.)

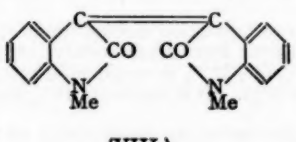

(VI.)

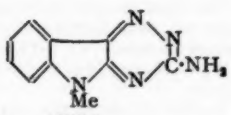
In this connection it is of interest that Marchlewski (*Ber.*, 1896, **29**, 1032) heated isatin β-semicarbazone with concentrated hydrochloric acid to 130° and obtained a substance difficultly soluble in all organic solvents which Borsche and Meyer (*Ber.*, 1921, **54**, 2849) suggested was di-isatin azine.

N-Methylisatin formed a precisely similar series of *syn*- and *anti*-β-guanylhydrazones and salts. Moreover when N-*methylisatin* anti-β-*guanylhydrazone* was acetylated it gave a *monoacetyl* derivative (VII) which on boiling with 16% hydrochloric acid gave not *N*-methylisatin azine but *NN'*-dimethyl*iso*indigotin (VIII) possibly through an intermediate azine.

Di-isatin azine and *NN'*-dimethyl*iso*indigotin when digested with boiling alcoholic phenylhydrazine furnished isatin β-phenylhydrazone and *N*-methylisatin β-phenylhydrazone respectively.


(VII.)


(VIII.)


(IX.)

N-*Methylisatin* syn-β-*guanylhydrazone* could be cyclised in the usual way by boiling in dilute ammoniacal solution to form 2-*amino*-9-*methyl*-1 : 3 : 4-*indotriazine* (IX) identical with the product of methylation of 2-amino-1 : 3 : 4-indotriazine with methyl sulphate and sodium methoxide in methyl alcoholic solution. The same substance was also formed by heating *N*-methylisatin *anti*-β-guanylhydrazone to 250° in a high vacuum.

The finding of Hantzsch–Werner stereoisomerism of oxime type among guanylhydrazones does not appear to have been recorded previously. There are, however, many instances of such isomerism among the phenylhydrazones and semicarbazones but in very few instances has it been found possible to assign *syn*- and *anti*-structures to the two forms isolated. In the present instance the formation of a cyclic derivative from one of the guanylhydrazones in boiling aqueous solution appears to fix the constitution of the *syn*-form, the *anti*-form only furnishing the same cyclic aminoindotriazine under much more drastic conditions, namely heat and sublimation in a vacuum at 250°.

Experimental.

Isatin syn-β-*Guanylhydrazone* (II).—Isatin (14·7 g.) and aminoguanidine hydrogen carbonate (13·7 g.) in acetic acid (500 c.c.) were boiled for 30 minutes and the solution then poured into water (1200 c.c.). The solution was then concentrated under reduced pressure to a small volume (200 c.c.) and the hydrazone (17·8 g.) collected. The mother-liquors were diluted with water and again concentrated and gave a further crop (1·5 g.). The hydrazone so prepared has m. p. 205° (efferv.); it resolidifies and is then unmelted at 300°.

If the conditions given by Rajagopalan (*loc. cit.*) are followed, the only difference from the above being that after dilution with water the solution is basified with excess of aqueous ammonia, then the same product is obtained.

As this β-guanylhydrazone is very difficult to purify as the base, it is better to convert it into the hydrochloride.

Isatin syn-β-*guanylhydrazone hydrochloride.* The combined crops of guanylhydrazone (19·3 g.) were dissolved in the calculated amount of hot N-hydrochloric acid and on cooling the solution gave the *hydrochloride* (16·6 g.), m. p. 278° (efferv.). For analysis a portion was crystallised from 10 volumes of N-hydrochloric acid and separated in needles, m. p. 280° (efferv.) (Found : C, 42·0, 42·3; H, 4·7, 4·9; Cl, 13·8; H_2O, 7·2. $C_9H_9ON_5,HCl,H_2O$ requires C, 41·9; H, 4·7; Cl, 13·8; H_2O, 7·0%).

The *nitrate* was prepared from an aqueous solution of the hydrochloride by addition of ammonium nitrate solution. It separated in thin prisms or needles which when crystallised from 10 volumes of water had m. p. 228° (vigorous decomp.) (Found : loss at 100°, 6·4. $C_9H_9ON_5,HNO_3,H_2O$ requires H_2O, 6·3%. Found on dried solid : C, 40·7; H, 3·9; N, 31·0. $C_9H_9ON_5,HNO_3$ requires C, 40·6; H, 3·8; N, 31·6%).

The *base* separated as fine yellow needles when a dilute solution (1%) of the hydrochloride was treated with excess 2N-ammonia solution. From more dilute solution it sometimes separated in plates. It is sparingly soluble in water or in dry acetone but readily soluble in moist acetone. It can be crystallised with difficulty from moist acetone and is unmelted at 310° but it may show some sintering about 200° or more frequently near 235° (Found on air-dried solid: loss at 100°, 4·1. $C_9H_9ON_5,0{\cdot}5H_2O$ requires H_2O, 4·2%. Found on dried solid: C, 53·1; H, 4·8; N, 33·8. $C_9H_9ON_5$ requires C, 53·2; H, 4·4; N, 34·5%).

Isatin anti-*β-Guanylhydrazone* (III).—Isatin *syn*-*β*-guanylhydrazone hydrochloride (25·8 g.) was treated with 0·5N-sodium hydroxide solution (400 c.c.) and heated on the water-bath at about 80° for 2 hours. The *base* first precipitated changed to a well crystallised orange solid, yield 21·0 g., m. p. 246° (efferv.). If dried at 110° it melts at 260° (efferv.). When crystallised from 30 volumes of spirit it separated in tablets, m. p. 246—248° with vigorous effervescence followed by crystallisation in prisms which are unmelted at 300° (Found: C, 48·9; H, 4·8; N, 31·9; H_2O, 8·3. $C_9H_9ON_5,H_2O$ requires C, 48·8; H, 5·0; N, 31·7; H_2O, 8·2%).

The *hydrochloride* crystallises in soft orange-yellow woolly needles which collapse with partial liquefaction at about 200° and then effervesce about 270° (Found: C, 41·5; H, 5·0; H_2O, 6·9. $C_9H_9ON_5,HCl,H_2O$ requires C, 41·9; H, 4·7; H_2O, 7·0%). The *nitrate* crystallises from water as a felt of pale yellow or pale orange needles: both forms may separate simultaneously in different parts of the solution. It is soluble in 5 parts of hot water and has m. p. 162° (efferv.) (Found: C, 38·1; H, 4·3; N, 29·9; H_2O, 6·1. $C_9H_9ON_5,HNO_3,H_2O$ requires C, 38·0; H, 4·3; N, 29·6; H_2O, 6·3%).

Acetylation of Isatin anti-*β-Guanylhydrazone.*—The parent base (1·0 g.) was boiled with acetic anhydride (10 c.c.) and two drops of pyridine for 5 minutes and gave a crystalline solid (1·39 g.), m. p. 207—212°. This was dissolved in methyl ethyl ketone (60 c.c.) and the product crystallised twice more from the same solvent; yield 0·58 g., m. p. 220—221°. *Diacetylisatin* anti-*β-guanylhydrazone* crystallises in clusters of prisms and is soluble in 120 parts of boiling methyl ethyl ketone and in 8 parts of boiling acetic anhydride. It is not soluble in 16% aqueous hydrochloric acid (Found: C, 54·8; H, 4·6. $C_{13}H_{13}O_3N_5$ requires C, 54·3; H, 4·6%). Satisfactory nitrogen analyses by micro-Dumas could not be obtained.

The first methyl ethyl ketone crystallisation mother-liquor on concentration gave a solid, m. p. 229°, which on two further crystallisations from fresh methyl ethyl ketone gave *monoacetylisatin* anti-*β-guanylhydrazone* (V), 0·12 g., m. p. 236—237°, in rectangular elongated leaflets (Found: C, 53·6; H, 4·9. $C_{11}H_{11}O_3N_5$ requires C, 53·8; H, 4·5%). It is soluble in 16% aqueous hydrochloric acid to an orange-red solution.

Better yields of the diacetyl derivative can be obtained by boiling for 15 minutes instead of 5 and recrystallisation of the product from acetic anhydride with 10 minutes' boiling at each recrystallisation. The final product from acetic anhydride always gives a redder melt than the product from methyl ethyl ketone. More prolonged boiling leads to darker solutions and decreasing yields.

Action of 16% *Hydrochloric Acid on the Diacetyl Derivative.*—The diacetyl compound (5·0 g.) was boiled with 16% hydrochloric acid (100 c.c.) for 2 hours. The deep red solid which had separated was collected by filtering the hot solution, yield 1·64 g. It was recrystallised from pyridine or from glacial acetic acid (50 c.c.) and gave maroon-coloured needles (1·12 g.), m. p. 300° (decomp.) (Found: C, 66·3, 66·2; H, 3·5, 4·0; N, 18·5, 18·7. Calc. for $C_{16}H_{10}O_3N_4$: C, 66·2; H, 3·4; N, 19·3%). It was soluble in concentrated sulphuric acid to a green-brown solution and in 2N-sodium hydroxide giving a red solution. These properties agree with those of di-isatin azine (VI), and a specimen of di-isatin azine prepared from isatin and hydrazine sulphate by Schapiro's method (*Ber.*, 1929, **62**, 2133) had identical properties.

When the di-isatin azine from the diacetyl product was boiled with phenylhydrazine in alcohol for 2 hours it gave isatin *β*-phenylhydrazone identified by mixed m. p. with authentic isatin *β*-phenylhydrazone and by analysis (Found: C, 71·0; H, 4·5. Calc. for $C_{14}H_{11}ON_3$: C, 70·9; H, 4·6%).

When di-isatin azine was boiled with 20 parts of acetic anhydride and 5 drops of pyridine for 45 minutes needles of the NN′-*diacetyl* derivative separated (Found: C, 64·5; H, 3·9; N, 15·5. $C_{20}H_{14}O_4N_4$ requires C, 64·2; H, 3·7; N, 15·0%).

Action of 16% *Hydrochloride Acid on Isatin* anti-*β-Guanylhydrazone.*—The base (1·0 g.) was boiled with 16% hydrochloric acid for several hours during which period a crystalline solid began to separate and increased in quantity on cooling; yield 1·3 g., m. p. 280° (efferv.). A portion was recrystallised from dilute hydrochloric acid and separated in well-formed yellow prisms, m. p. 276° (decomp.). A mixture with isatin *syn*-*β*-guanylhydrazone hydrochloride also decomposed at the same temperature. It was dissolved in 20 parts of water and treated with concentrated ammonium nitrate solution. The nitrate separated in needles, m. p. 229°, with vigorous decomposition. The properties were precisely those of the *syn*-nitrate.

Isatin syn-*β-Guanylhydrazone-5-sulphonic Acid.*—Isatin *syn*-*β*-guanylhydrazone base was treated with dilute sulphuric acid and the yellow needles of the sulphate, unmelted at 300°, were collected and dried and then heated on a water-bath with sulphuric acid for 8 hours. On pouring into water the *sulphonic acid* separated and was purified by solution in dilute ammonia and precipitation with acetic acid. It separated in yellow needles, unmelted at 340° (Found in solid dried at 110°: C, 35·9; H, 3·8; N, 23·2. $C_9H_9O_4N_5S,H_2O$ requires C, 35·9; H, 3·7; N, 23·3%).

When isatin *anti*-*β*-guanylhydrazone (2 g.) was added to sulphuric acid (5 c.c.) and heated on the water-bath the deep yellow original solution became red and after 8 hours' heating the reaction mixture was worked up in the same way as in the preceding preparation. Yellow needles were obtained, unmelted at 340° (Found on solid dried at 110°: C, 36·1; H, 3·5; N, 23·4. Calc. for $C_9H_9O_4N_5S,H_2O$: C, 35·9; H, 3·7; N, 23·3%). Comparison of the properties of this sulphonic acid and of its sodium, ammonium, and calcium salts with those of the preceding acid showed that the two acids were identical.

N-*Methylisatin* syn-*β-Guanylhydrazone.*—*N*-Methylisatin (16·1 g.) and aminoguanidine hydrogen carbonate (13·7 g.) were boiled in glacial acetic acid (500 c.c.) for 30 minutes. The solution was poured into water, concentrated at 50° to a small volume, and excess of 2N-ammonia solution added. The yellow crystalline precipitate (22·0 g.) was collected, m. p. 210°. It was converted into a very sparingly

soluble ***hydrochloride*** in quantitative yield. A sample crystallised from a large volume of boiling water had m. p. 312° (Found: C, 47·0; H, 4·4; N, 27·5. $C_{10}H_{11}ON_5$,HCl requires C, 47·2; H, 4·7; N, 27·6%). The ***base*** obtained by the action of aqueous ammonia on the hydrochloride crystallised from methyl ethyl ketone in small yellow needles, m. p. 232° (decomp.) (Found: C, 55·3; H, 5·1; N, 32·1. $C_{10}H_{11}ON_5$ requires C, 55·3; H, 5·1; N, 32·2%).

N-Methylisatin anti-*β-Guanylhydrazone*.—The above hydrochloride (2·71 g.) was treated with 0·5N-sodium hydroxide solution (50 c.c.) on the boiling water-bath for 8 hours. The anti-***base*** (2·36 g.) separated in tablets which crystallised from spirit (185 c.c.) with the addition of a drop of water in large elongated leaflets, m. p. 274° (efferv.) but becoming opaque at 235° (Found on 2 different preparations: C, 53·3, 53·8; H, 5·2, 5·3; N, 30·4, 31·1. $C_{10}H_{11}ON_5$,0·5H_2O requires C, 53·1; H, 5·3; N, 31·0%).

The ***hydrochloride*** crystallised in fine yellow needles, m. p. 312° (decomp.) (Found on solid dried at 100°: C, 47·2; H, 4·5; N, 28·0. $C_{10}H_{11}ON_5$,HCl requires C, 47·3; H, 4·7; N, 27·6%).

Acetyl-N-methylisatin anti-*β-Guanylhydrazone* (VII).—The base (0·5 g.) was boiled with acetic anhydride (5 c.c.) and pyridine (2 drops) for 5 minutes. The product [0·55 g., m. p. 238° (decomp.)] was dissolved in boiling methyl ethyl ketone (125 c.c.) and separated in long needles of the ***acetyl*** derivative which slowly changed to small plates, yield 0·5 g., m. p. 237° (decomp.) (Found: C, 54·0; H, 5·4. $C_{12}H_{12}O_2N_5$,0·5H_2O requires C, 53·7; H, 5·3%). The water of crystallisation was not lost at 140° and micro-Dumas estimates of nitrogen gave very low values. On hydrolysis on the water-bath with 0·5N-aqueous sodium hydroxide the parent base was obtained in elongated leaflets, m. p. 270° not depressed by the pure *anti*-base. If crystallised from acetic acid it retained one molecule of acetic acid after drying at 85° (Found: C, 52·6; H, 5·3; N, 22·1. $C_{12}H_{13}O_2N_5$,$C_2H_4O_2$ requires C, 52·7; H, 5·3; N, 22·0%).

Action of 16% ***hydrochloric acid***. The acetyl compound (6·4 g.) was boiled for 30 hours with 16% hydrochloric acid (100 c.c.). The red solid was collected; yield 2·4 g. It crystallised from pyridine or from acetone in deep red needles, m. p. 268° (Found: C, 74·1; H, 4·8; N, 9·6. Calc. for $C_{18}H_{14}O_2N_2$: C, 74·5; H, 4·8; N, 9·7%). It could also be purified by sublimation in a high vacuum and was identified as *NN'*-dimethyl*iso*indigotin (VIII) by comparison with an authentic specimen prepared either by Stollé's method (*J. pr. Chem.*, 1930, **128**, 35) or by condensation of *N*-methylisatin with *N*-methyloxindole. On boiling with phenylhydrazine in alcohol it gave *N*-methylisatin *β*-phenylhydrazone, m. p. 136°, as did authentic *N*-methyl*iso*indigotin and a mixture showed no depression of m. p.

Preparation of 2-*Amino*-1 : 3 : 4-*indotriazine* (IV).—Isatin *syn-β*-guanylhydrazone hydrochloride (25·3 g.) was dissolved in water (5 l.) and ammonia solution (*d* 0·88) added in slight excess. The solution was boiled for 6 hours, and the solid which had separated during the boiling was collected whilst the solution was still hot. It consisted of buff-coloured prisms, yield 12·7 g., unmelted at 300°. It was converted into the ***hydrochloride***, pale yellow slender needles, m. p. 324° (efferv.) (Found in solid dried at 105°: C, 49·1; H, 3·6; N, 31·5. $C_9H_7N_5$,HCl requires C, 48·8; H, 3·6; N, 31·6%). The corresponding ***nitrate*** separated from dilute nitric acid in pale yellow prisms, m. p. 228° (Found in solid dried at 105°: C, 43·7; H, 3·5; N, 33·4. $C_9H_7N_5$,HNO_3 requires C, 43·5; H, 3·2; N, 33·9%). The ***base*** crystallised from pyridine in tiny colourless needles, m. p. 350—354° (decomp.) (Found: C, 58·3; H, 3·9; N, 38·1. $C_9H_7N_5$ requires C, 58·4; H, 3·8; N, 37·8%). It sublimes readily on heating in a high vacuum. It is sparingly soluble in water and all organic solvents but readily souble in hot aqueous sodium hydroxide solution and separates unchanged on cooling.

2-Amino-1 : 3 : 4-indotriazine is also formed from isatin *anti-β*-guanylhydrazone by heating to 250° in a high vacuum (0·3 mm.) and sublimes out slowly.

2-*Acetamido*-9-*acetyl*-1 : 3 : 4-*indotriazine*.—2-Amino-1 : 3 : 4-indotriazine (1·85 g.) was refluxed with acetic anhydride (50 c.c.) and 1 drop of pyridine for 30 minutes. The crystalline product (2·6 g.) which began to separate during the boiling was collected when the solution was cool and was crystallised from glacial acetic acid from which it separated in colourless prisms, m. p. 283°. 2-*Acetamido*-9-*acetyl*-1 : 3 : 4-*indotriazine* could be sublimed without residue in a high vacuum at 250° (Found: C, 57·8; H, 4·3; N, 26·2. $C_{13}H_{11}O_2N_5$ requires C, 58·0; H, 4·1; N, 26·0%).

2-*Amino*-1 : 3 : 4-*indotriazine*-6-*sulphonic Acid*.—The above triazine (IV) (5 g.) was dissolved in sulphuric acid and the solution heated on the water-bath for 8 hours. On pouring into water, the ***sulphonic acid*** (7·8 g.) separated in yellow needles, unmelted at 310° (Found: C, 38·6; H, 3·4; N, 24·9. $C_9H_7O_3N_5S$,H_2O requires C, 38·2; H, 3·2; N, 24·7%). The ***sodium*** salt crystallised from water in colourless prisms, unmelted at 300° (Found: Na, 7·6. $C_9H_6O_3N_5SNa$ requires Na, 8·0%). The calcium and ammonium salts were also colourless. The free sulphonic acid is precipitated on the addition of acetic acid to the aqueous solution of the sodium salt.

The corresponding ***sulphonamide*** was prepared by warming the sulphonic acid in chlorosulphonic acid to 80° for 1½ hours, pouring on to ice, collecting the solid and grinding with concentrated ammonia solution. It was purified by precipitation from solutions of its hydrochloride in water by the addition of ammonia solution and was obtained as small colourless prisms, unmelted at 320° (Found: C, 40·9; H, 2·9. $C_9H_8O_2N_6S$ requires C, 40·9; H, 3·0%).

Preparation of 2-*Amino*-9-*methyl*-1 : 3 : 4-*indotriazine* (IX).—This preparation was carried out in the same way as that of its unmethylated homologue (above). The ***hydrochloride*** crystallised from dilute hydrochloric acid in pale yellow slender needles which retained water of crystallisation when dried at 105° (Found: C, 47·7; H, 4·7; N, 27·8. $C_{10}H_9N_5$,HCl,H_2O requires C, 47·3; H, 4·7; N, 27·6%). The ***base*** could be crystallised from pyridine but was best purified by sublimation in a high vacuum and thus obtained in colourless prisms, m. p. 314° (Found: C, 59·9; H, 4·5; N, 35·5. $C_{10}H_9N_5$ requires C, 60·3; H, 4·5; N, 35·2%). Unlike its lower homologue it is insoluble in dilute sodium hydroxide solution. The ***nitrate*** separated from dilute nitric acid in long, pale yellow needles, m. p. 210° (decomp.) (Found: N, 31·8; $C_{10}H_9N_5$,HNO_3 requires N, 32·1%).

2-Amino-9-methyl-1 : 3 : 4-indotriazine was also obtained by heating *N*-methylisatin *anti-β*-guanylhydrazone in a high vacuum in a sublimation apparatus to 250°. The product had to be resublimed several times and was finally extracted with boiling acetone which removed a soluble red solid, m. p. 268°, which proved to be *NN'*-dimethyl*iso*indigotin. The insoluble solid was resublimed and was then shown

by mixed m. p. determinations on the base and salts to be identical with 2-amino-9-methyl-1 : 3 : 4-indotriazine.

Methylation of 2-Amino-1 : 3 : 4-indotriazine.—This triazine (2 g.) was dissolved in excess of a solution of sodium methoxide in methyl alcohol (100 c.c.) and freshly distilled dimethyl sulphate (5 c.c.) was gradually added. The reaction was completed by heating on the water-bath for 2 hours during which period a green solid separated. It was crystallised from pyridine and found to be 2-amino-9-methyl-1 : 3 : 4-indotriazine (0·5 g.) identical with the previously described material. Unmethylated triazine (1·2 g.) was recovered from the methyl alcoholic mother liquor by acidification with acetic acid.

We are indebted to Dr. F. G. Mann, F.R.S., for *N*-methyloxindole, and to Imperial Chemical Industries Ltd. for a specimen of oxindole.

NATIONAL INSTITUTE FOR MEDICAL RESEARCH,
HAMPSTEAD, N.W. 3.

[*Received, March 11th,* 1948.]

NOTES.

The Synthesis of 1 : 3-*Dihydroxyphenazine.*

By G. R. CLEMO and A. F. DAGLISH.

HEGEDÜS (*Chem. Abs.*, 1947, **41**, 6252) has prepared 1 : 2-dihydroxyphenazine whose diacetoxy-derivative is different from that obtained from the pigment of *Chromobacterium iodinum* (Clemo and McIlwain, *J.*, 1938, 479).

In the course of synthetic work in this field, which will be fully reported later, we have prepared 1 : 3-dihydroxyphenazine by the hydrolysis of 1 : 3-diaminophenazine (Albert and Duewell, *J. Soc. Chem. Ind.*, 1947, **66**, 11). Although this melts at 275°, its m. p. is depressed to 250° by the dihydroxyphenazine from the pigment and its alcoholic solution gives a brown coloration with ferric chloride and no lake with alcoholic lead acetate.

1 : 3-*Dihydroxyphenazine.*—1 : 3-Diaminophenazine (1·0 g.) and dilute sulphuric acid (60 ml.; 3N) were heated in a sealed tube at 180° for 4 hours, the product diluted with an equal volume of water, and neutralised with sodium hydrogen carbonate. The crystalline precipitate was collected, extracted with aqueous sodium hydroxide, the resulting blue solution treated with sulphur dioxide, and the brown precipitate collected, dried, and sublimed at 170°/0·1 mm. The sublimate was recrystallised from alcohol, yielding the *dihydroxy*-compound in orange-red needles (0·2 g.), m. p. 275° (Found: C, 67·6; H, 4·1; N, 13·4. $C_{12}H_8O_2N_2$ requires C, 67·9; H, 3·8; N, 13·2%).

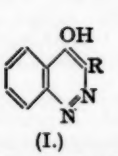
1 : 3-*Diacetoxyphenazine.*—1 : 3-Dihydroxyphenazine (15 mg.) was refluxed for 1 hour in pyridine (1·5 ml.) and acetic anhydride (6 drops), the solvent removed under reduced pressure, and the residue crystallised from alcohol; white needles of the *diacetoxy*-derivative separated, m. p. 163° (Found: C, 65·2; H, 4·6. $C_{16}H_{12}O_4N_2$ requires C, 64·9; H, 4·1%).

One of us (A. F. D.) is indebted to the Ministry of Education and Durham County Education Committee for maintenance grants, and our thanks are due to Mr. W. A. Campbell for making the micro-analyses.—KING'S COLLEGE, UNIVERSITY OF DURHAM, NEWCASTLE-UPON-TYNE.
[*Received, January 19th,* 1948.]

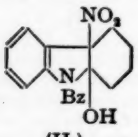
Cinnolines. Part XX. 4-Hydroxy-3-ethylcinnoline and 3-4′-Hydroxy-3′-cinnolyl-n-propane-1-carboxylic Acid.

By J. R. KENEFORD and J. C. E. SIMPSON.

THE synthesis of 3-substituted 4-hydroxycinnolines (as I; R = CH_2CO_2H, Me, and halogen) from the appropriate *o*-aminoacetophenones, *o*-$NH_2{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2R$, has already been described (Schofield and



(I.)



(II.)

Simpson, *J.*, 1945, 520; this vol., p. 1170; Keneford and Simpson, *ibid.*, p. 354). The preparation of the two compounds named in the title by the same reaction was undertaken in order to examine the scope of this method for the synthesis of analogues containing higher alkyl groups attached to C_3. *o*-Aminobutyrophenone, required for (I; R = Et), and originally prepared from butyryl chloride by Elson, Gibson, and Johnson (*J.*, 1930, 1128) in 8·6% yield, was obtained from butyric anhydride in 28% yield by suitable modifications; and 5-keto-5-2′-aminophenyl-*n*-pentane-1-carboxylic acid (δ-*o*-aminobenzoylvaleric acid), the precursor of [I; R = $[CH_2]_3{\cdot}CO_2H$], is obtainable, *via* the *N*-benzoyl derivative, from (II) (Perkin and Plant, *J.*, 1923, 676). Each amino-ketone was readily converted, by diazotisation in concentrated hydrochloric acid and cyclisation, into the corresponding 3-substituted cinnoline (I; R = Et and $[CH_2]_3{\cdot}CO_2H$).

o-*Aminobutyrophenone.*—Butyrophenone, b. p. 128°/30 mm. (yield, 90%), was obtained from benzene (300 c.c.), aluminium chloride (294 g.), and *n*-butyric anhydride (160 c.c., added during 1 hour with stirring); the reaction was started at room temperature, allowed to proceed without cooling, and completed by heating on the steam-bath for ½ hour. Elson, Gibson, and Johnson (*loc. cit.*) record 66%

yield using butyryl chloride. The ketone (60 c.c.) was mixed with acetic acid (8 c.c.) and added during ½ hour to stirred nitric acid (300 c.c., *d* 1·5) at 0° ±2°. After a further ½ hour the solution was poured on ice (1200 g.), and the solid collected; *m*-nitrobutyrophenone, m. p. 62—63° (all m. p.s are uncorrected), was obtained by crystallisation from alcohol, and crude *o*-nitro-ketone from the alcoholic mother liquor and also from the basified aqueous acid filtrate; 415 g. of butyrophenone gave 238·5 g. (43·5%) of *m*-nitro-ketone and 247 g. (45%) of crude *o*-nitro-ketone. The latter (25 g.), mixed with concentrated hydrochloric acid (45 c.c.), was treated with granulated tin (26 g.) during ½ hour with addition of more acid (70 c.c.), and finally heated for ½ hour on the steam-bath; the *o*-aminobutyrophenone, isolated by basification and steam-distillation, had b. p. 165—170°/26—28 mm. [161·5 g. (62%) from 310 g. of nitro-ketone]. o-*Acetamidobutyrophenone*, prepared from the amine (50 g.) and acetic anhydride (100 c.c.) at 95° for 1 hour (crude yield, 66 g.), crystallised from ligroin (b. p. 40—60°) in long, lustrous, prismatic needles, m. p. 46—47°, evidently containing a little impurity (Found: C, 70·9; H, 7·4. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·35%).

4-*Hydroxy*-3-*ethylcinnoline*.—A solution of *o*-aminobutyrophenone (1·65 g., regenerated from the acetamido-compound by acid hydrolysis) in hydrochloric acid (10N, 200 c.c.) was diazotised (0·8 g. of sodium nitrite in 1·25 c.c. of water), the diazonium solution kept at 50—60° for 2 hours, concentrated (reduced pressure) to a small volume, and treated with aqueous sodium acetate, and the solid (1·2 g., 68%; m. p. 225°) collected. Crystallisation from acetic acid gave 4-*hydroxy*-3-*ethylcinnoline* as clumps of colourless, opaque rods, m. p. 225—226° (Found: C, 69·0; H, 5·6; N, 16·0. $C_{10}H_{10}ON_2$ requires C, 68·95; H, 5·8; N, 16·1%).

Preparation and Hydrolysis of 11-*Nitro*-10-*hydroxy*-9-*benzoylhexahydrocarbazole*.—A stirred solution of 9-benzoyl-1 : 2 : 3 : 4-tetrahydrocarbazole (20 g.; Perkin and Plant, *loc. cit.*, p. 685) in acetic acid (55 c.c.) at 30° was treated with nitric acid (6 c.c., *d* 1·42). The temperature rose to 50°, and the yellow 11-nitro-10-hydroxy-9-benzoylhexahydrocarbazole, which separated after a few seconds, was collected and washed with a little acetic acid [13·2 g. (53%), m. p. 149° (decomp.)]; this method, using a smaller volume of acetic acid than that used by Perkin and Plant, who give m. p. 150° (decomp.), gives an improved yield. Hot alkaline hydrolysis of this compound to 5-keto-5-2′-benzamidophenyl-*n*-pentane 1-carboxylic acid, using the conditions of Perkin and Plant, gave a product of inferior quality and in poorer yield than that of these authors, who give m. p. 126° and 56% yield. In the best of several variations, a solution of the nitro-compound (5 g.) in 5% potassium hydroxide (125 c.c., made up in 50% aqueous alcohol) was left at room temperature for 2 hours; dilution and acidification gave crude benzamido-acid (1·87 g., 39%; m. p. 120—122°). This acid was unchanged after ½ hour's refluxing with 5N-hydrochloric acid; hydrolysis of the acid (6 g.) in hot aqueous potassium hydroxide according to the conditions of Perkin and Plant (*loc. cit.*) gave 5-keto-5-2′-aminophenyl-*n*-pentane-1-carboxylic acid, m. p. 123—126°; yield, 2·25 g. Perkin and Plant record m. p. 129° and 3·5 g.

3-4′-*Hydroxy*-3′-*cinnolyl*-n-*propane*-1-*carboxylic Acid*.—The above amino-acid (2·25 g.) was dissolved in hydrochloric acid (10N, 450 c.c.) and treated with a solution of sodium nitrite (0·77 g.) in water (1 c.c.) at 0—5°. The solution was filtered from sodium chloride, kept for 6 hours at 50—55°, concentrated to a small volume (reduced pressure), decanted from a little oil which had separated, and treated with excess of aqueous sodium acetate. The crude solid (1·27 g., m. p. 170—185°) was crystallised from acetic acid, from which 3-4′-*hydroxy*-3′-*cinnolyl*-n-*propane*-1-*carboxylic acid* separated in fawn-coloured, lustrous blades, m. p. 201·5—202·5° [Found (two samples): C, 60·6, 60·8; H, 5·4, 5·15; N, 11·9. $C_{12}H_{12}O_3N_2,\frac{1}{2}H_2O$ requires C, 60·45; H, 5·35; N, 11·75%].

We are indebted to the Medical Research Council for a Research Studentship (J. R. K.).—WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY, LIVERPOOL SCHOOL OF TROPICAL MEDICINE. [*Received, February 3rd*, 1948.]

The Formation of Ketones from Semicarbazones by the Action of Nitrous Acid.

By D. H. HEY and D. S. MORRIS.

IN a recent publication (*Rec. Trav. chim.*, 1946, **65**, 796), Goldschmidt and Veer have reported that carbonyl compounds can be regenerated in good yield from semicarbazones by treatment with sodium nitrite in glacial acetic acid solution. In this manner acetophenone, *trans*-dehydroandrosterone acetate, and pregnenolone acetate were regenerated from their semicarbazones, and the method is stated to have particular advantages for the fission of semicarbazones of the *cyclo*pentanohydrophenanthrene series. Wolfrom (*ibid.*, 1947, **66**, 238) claims to have used the method previously for the regeneration of *aldehydo*-sugar acetates from the corresponding *aldehydo*-penta-acetate semicarbazones (*J. Amer. Chem. Soc.*, 1934, **56**, 1794). This work was considered as an extension of the work of Claisen and Manasse (*Ber.*, 1889, **22**, 530) on the conversion of *iso*nitrosocamphor into camphorquinone, a view which is contested by Goldschmidt and Veer (*Rec. Trav. chim.*, 1947, **66**, 238).

A similar method, used by the authors in 1943 under somewhat different experimental conditions, was suggested by the work of Harries (*Ber.*, 1901, **34**, 1494), who used nitrous acid to regenerate succindialdehyde from its oxime (cf. Robinson, *J.*, 1917, 766). The following examples illustrate the method:

(i) Nitrous fumes, generated from sodium nitrite and dilute sulphuric acid, were passed into a suspension of *cyclo*hexanone semicarbazone (10 g.) in water (200 c.c.) until a clear solution was obtained. The solution was extracted with ether and the extract washed with water and dried. Evaporation of the solvent and distillation of the residue gave *cyclo*hexanone (5·8 g.), b. p. 155°.

(ii) A suspension of cholest-4-enone semicarbazone (1·1 g., m. p. 228—230°) in water (10 c.c.) and benzene (10 c.c.) was treated with nitrous fumes, prepared as above. The benzene layer became almost clear. The aqueous layer was removed, and the benzene solution washed with dilute sodium hydrogen carbonate solution and with water, and dried. Evaporation of the benzene left a crystalline residue (1·0 g., m. p. 65—70°). Recrystallisation from methyl alcohol–ether gave pure cholest-4-enone (0·5 g.), m. p. and mixed m. p. 79—80°.

(iii) By the same procedure as in (ii) above, *trans*-dehydroandrosterone acetate semicarbazone [0·20 g., m. p. 266—267° (uncorr.)] gave *trans*-dehydroandrosterone acetate [0·15 g., m. p. 164° (uncorr.)]. —BRITISH SCHERING RESEARCH INSTITUTE, ALDERLEY EDGE, CHESHIRE. [*Received, February 16th*, 1948.]

The Preparation of Certain Urethanes and Their Conversion into N-*Nitroso-derivatives. Some Chloronitro-compounds of the Type* $CRR'Cl\cdot CCl(NO_2)R''$. By A. F. CHILDS, L. J. GOLDSWORTHY, G. F. HARDING, S. G. P. PLANT, and G. A. WEEKS.

NITROSOURETHANES have long been known to possess vesicant properties, and the members of this class, and their intermediates, now described were prepared as part of an investigation designed to examine this feature more fully. A study of the properties of compounds of the type $CRR'Cl\cdot CCl(NO_2)R''$ has involved the preparation of some examples not hitherto recorded.

Hydrochloride of 2-Chloro-2′-aminodiethyl Sulphide.—2-Chloroethylamine hydrochloride (23·2 g., prepared by the method of Ward, *J. Amer. Chem. Soc.*, 1935, **57**, 914) was added to a solution of monothioethylene glycol (15·6 g.) in aqueous potassium hydroxide (40 c.c. of 5N), and the whole treated during 10 minutes, with stirring, with more alkali (40 c.c. of 5N). After being heated for an hour at 100°, the mixture was cooled, acidified with concentrated hydrochloric acid, and evaporated under reduced pressure. The hydrochloride of 2-amino-2′-hydroxydiethyl sulphide was extracted from the residue with alcohol, and recovered as a pale brown syrup (30 g.) on evaporation of the filtered extract. A solution of thionyl chloride (34 g.) in chloroform (25 c.c.) was gradually added to a mechanically stirred suspension of this salt in chloroform (25 c.c.), and the temperature was kept at 50° until the reaction was completed. The hydrochloride of 2-chloro-2′-aminodiethyl sulphide (26 g.), isolated by evaporation of the mixture and purified by crystallisation from chloroform, was very hygroscopic and melted at 68—70° (compare Gabriel and Colman, *Ber.*, 1912, **45**, 1643).

*Methyl 2-Chloro-*n*-propylcarbamate and Other Urethanes.*—A mixture of 2-chloro-*n*-propylamine hydrochloride (32 g., prepared by the method of Abderhalden and Eichwald, *Ber.*, 1918, **51**, 1312), dissolved in water (70 c.c.), and methyl chloroformate (23·4 g.), dissolved in ether (80 c.c.), was mechanically stirred and kept below 5° while a solution of potassium hydroxide (27·6 g.) in water (200 c.c.) was gradually added. After a further 15 minutes, the ether layer and additional ether extracts were dried ($MgSO_4$), and fractionated. *Methyl 2-chloro-*n*-propylcarbamate* (25·5 g.) was obtained as a colourless oil, b. p. 118—119°/22 mm. (Found: C, 39·9; H, 6·9; Cl, 22·1. $C_5H_{10}O_2NCl$ requires C, 39·6; H, 6·6; Cl, 23·4%).

The following were prepared by methods which were essentially similar to the above: *Methyl allylcarbamate* (from allylamine hydrochloride), colourless oil, b. p. 179·5—183°/748 mm. (Found: C, 51·6; H, 8·0; N, 12·6. $C_5H_9O_2N$ requires C, 52·2; H, 7·8; N, 12·2%); *methyl 3-chloro-*n*-propylcarbamate* (from 3-chloro-*n*-propylamine hydrochloride, obtained by the action of thionyl chloride on the hydrochloride of 3-hydroxy-*n*-propylamine prepared by Putochin's method, *Ber.*, 1926, **59**, 625), colourless oil, b. p. 131°/20 mm. (Found: N, 9·3. $C_5H_{10}O_2NCl$ requires N, 9·2%); ethyl 2-chloroethylcarbamate (from 2-chloroethylamine hydrochloride and ethyl chloroformate), colourless oil, b. p. 117°/19 mm. (Found: C, 39·9; H, 6·8%), previously prepared by Wenker (*J. Amer. Chem. Soc.*, 1936, **58**, 2608) by the action of thionyl chloride on ethyl 2-hydroxyethylcarbamate; *methyl 2-(2-chloroethylthio)ethylcarbamate*, $CH_2Cl\cdot CH_2\cdot S\cdot CH_2\cdot CH_2\cdot NH\cdot CO_2Me$ (from the hydrochloride of 2-chloro-2′-aminodiethyl sulphide), colourless liquid, b. p. 120—130°/0·1 mm. (Found: N, 7·1. $C_6H_{12}O_2NClS$ requires N, 7·1%); *NN′-dicarbomethoxy-2 : 2′-diaminodiethyl sulphide* (from 2 : 2′-diaminodiethyl sulphide; Nathan and Bogert, *J. Amer. Chem. Soc.*, 1941, **63**, 2361), colourless prisms, m. p. 71—72°, from water (Found: N, 12·5. $C_8H_{16}O_4N_2S$ requires N, 11·9%) (ether extraction was here unnecessary, the crude product being collected by filtration); *methyl* s-*trichloro-*tert.*-butylcarbamate*, $(CH_2Cl)_3C\cdot NH\cdot CO_2Me$ (from *s*-trichloro-*tert*.-butylamine hydrochloride; Kleinfeller, *Ber.*, 1929, **62**, 1582), colourless plates, m. p. 82°, from aqueous alcohol (Found: C, 31·0; H, 4·6; Cl, 45·3. $C_5H_{10}O_2NCl_3$ requires C, 30·7; H, 4·3; Cl, 45·4%), and the corresponding *ethyl* ester, colourless plates, m. p. 79°, from aqueous alcohol (Found: C, 34·2; H, 4·8; N, 5·7; Cl, 41·9. $C_7H_{12}O_2NCl_3$ requires C, 33·8; H, 4·8; N, 5·6; Cl, 42·9%).

*Methyl 2 : 3-Dichloro-*n*-propylcarbamate.*—A molecular proportion of chlorine in carbon tetrachloride solution was gradually added to methyl allylcarbamate below 15°. When the solution was washed with water, dried ($MgSO_4$), and fractionated, *methyl 2 : 3-dichloro-*n*-propylcarbamate* was obtained as an oil, b. p. 139—140°/12 mm., which slowly solidified. It then separated from aqueous alcohol in colourless needles, m. p. 55—56° (Found: Cl, 37·9. $C_5H_9O_2NCl_2$ requires Cl, 38·2%). The yield was 70% of the theoretical.

Methyl N-*Nitroso-2-chloro-*n*-propylcarbamate,* $CH_2\cdot CHCl\cdot CH_2\cdot N(NO)\cdot CO_2Me$, *and Other Nitrosourethanes.*—Nitrous fumes, generated by the action of 56% nitric acid on arsenious oxide and freed from nitric acid by passage through a spiral condenser surrounded by ice, were passed into a solution of methyl 2-chloro-*n*-propylcarbamate (10 g.) in an equal volume of ether at 0° until the colour became blue. Most of the excess of oxides of nitrogen was removed by aspiration with air, more ether was added, and the whole shaken twice with ice-cold dilute sodium carbonate solution. After being dried ($MgSO_4$), the ether was removed under reduced pressure at 40°, and *methyl N-nitroso-2-chloro-*n*-propylcarbamate* (10·4 g.) obtained as a reddish-yellow oil (Found: C, 33·6; H, 5·2; N, 15·9; Cl, 18·9. $C_5H_9O_3N_2Cl$ requires C, 33·2; H, 5·0; N, 15·5; Cl, 19·7%).

The following were similarly prepared from the appropriate carbamates as reddish-yellow oils (except where otherwise stated) which could not be distilled: *Methyl N-nitroso-3-chloro-*n*-propylcarbamate* (Found: N, 16·1%); *ethyl N-nitroso-2-chloroethylcarbamate* (Found: C, 33·8; H, 5·1%); *methyl N-nitroso-2 : 3-dichloro-*n*-propylcarbamate* (nitrosation proceeded much more slowly in this case, and the ethereal solution containing nitrous fumes was left for two days at room temperature before the product was isolated) (Found: C, 28·4; H, 4·0; N, 13·1. $C_5H_8O_3N_2Cl_2$ requires C, 27·9; H, 3·7; N, 13·0%); *methyl N-nitroso-2-(2-chloroethylthio)ethylcarbamate*, $CH_2Cl\cdot CH_2\cdot S\cdot CH_2\cdot CH_2\cdot N(NO)\cdot CO_2Me$ (Found: N, 12·3. $C_6H_{11}O_3N_2ClS$ requires N, 12·4%); *NN′-dinitroso-NN′-dicarbomethoxy-2 : 2′-diaminodiethyl sulphide*, $S[CH_2\cdot CH_2\cdot N(NO)\cdot CO_2Me]_2$, small, pale yellow plates, m. p. 104—105°, from

alcohol (Found: N, 18·7. $C_8H_{14}O_6N_4S$ requires N, 19·0%). Methyl allylcarbamate could not be made to give a pure specimen of the corresponding nitroso-compound under similar conditions, probably owing to reaction with the double link. Methyl and ethyl *s*-trichloro-*tert.*-butylcarbamate were unreactive and could not be converted into nitroso-compounds with nitrous fumes or nitrosyl chloride under various conditions.

Methyl N-*Nitroso*-2-*bromoethylcarbamate*.—An ethereal solution of methyl 2-bromoethylcarbamate was prepared from 2-bromoethylamine hydrobromide (Cortese, *J. Amer. Chem. Soc.*, 1936, **58**, 191) and methyl chloroformate by the general method described above, but an attempt to distil the urethane under reduced pressure resulted in elimination of methyl bromide and formation of 2-oxazolidone. Conversion into *methyl* N-*nitroso*-2-*bromoethylcarbamate* with nitrous fumes was effected as in analogous cases, except that the ether was removed under reduced pressure at room temperature, leaving the product as a reddish-yellow oil (Found: N, 12·9. $C_4H_7O_3N_2Br$ requires N, 13·3%).

2-*Chloroethylcyanamide*, $CH_2Cl{\cdot}CH_2{\cdot}NH{\cdot}CN$.—Potassium hydroxide (25·2 g.) in a very little water was gradually added to a vigorously stirred mixture of 2-chloroethylamine hydrochloride (29·3 g.) and a solution of cyanogen bromide (26·8 g.) in ether (150 c.c.), the whole being cooled in ice-water. After the precipitated potassium salts had been filtered off, the ethereal layer was dried ($MgSO_4$), and fractionated. 2-*Chloroethylcyanamide* was collected at 82°/0·1 mm. as a colourless oil (Found: N, 26·7. $C_3H_5N_2Cl$ requires N, 26·8%). The yield was about 60% of the theoretical. It could not be converted into an *N*-nitroso-derivative.

Methyl N-*Nitro*-2-*chloroethylcarbamate*.—Methyl 2-chloroethylcarbamate (16 g.) was added dropwise to nitric acid (37 c.c., *d* 1·5) which was mechanically stirred and cooled in ice-water. With continued stirring and cooling, the whole was made just alkaline by the gradual addition of concentrated aqueous sodium carbonate, and the oily product was extracted with ether. After the extract had been washed with water, dried, and filtered, the solvent was removed by aspiration with air under reduced pressure, and *methyl* N-*nitro*-2-*chloroethylcarbamate* obtained as a yellow oil (Found: N, 15·4. $C_4H_7O_4N_2Cl$ requires N, 15·3%). This type of compound cannot be distilled without decomposition (van Erp, *Rec. Trav. chim.*, 1895, **14**, 1).

2-*Imino-oxazolidine*.—A solution of 2-chloroethylamine hydrochloride (11·6 g.) and potassium cyanate (8·1 g.) in water (20 c.c.) was refluxed for 1½ hours, cooled, and treated with alcohol (100 c.c.) to precipitate potassium chloride. After filtration, the filtrate was evaporated under reduced pressure and the residue dissolved in a small amount of alcohol. When the whole had been again filtered and the solution evaporated, the residue was found to contain 16·6% of chloride ion. That the material contained a high proportion of 2-imino-oxazolidine hydrochloride was proved by dissolving it (0·5 g.) in hot water and adding hot aqueous sodium picrate (1 g.). After recrystallisation from water, the product which separated melted at 186—188° (Found: C, 34·6; H, 3·0. Calc. for $C_9H_9O_8N_5$: C, 34·3; H, 2·9%). This was obviously identical with the picrate of 2-imino-oxazolidine described by Gabriel (*Ber.*, 1889, **22**, 1139). Evidently 2-chloroethylurea is unstable, a fact which is not surprising in view of the similar transformations observed with the corresponding bromo- and iodo-compounds (Gabriel, *loc. cit.*; *Ber.*, 1917, **50**, 826; Birckenbach and Linhard, *ibid.*, 1931, **64**, 1076).

1 : 2 : 3-*Trichloro*-2-*nitropropane*.—When 2-chloro-2-nitro-1 : 3-dihydroxypropane (61 g., prepared as described by Schmidt and Wilkendorf, *Ber.*, 1922, **55**, 316) was intimately mixed with phosphorus pentachloride (170 g.), a vigorous reaction soon set in with evolution of hydrogen chloride. After this had subsided, the mixture was refluxed for 3½ hours and then slowly poured into warm water (500 c.c.), the temperature being kept well below 100°. The 1 : 2 : 3-*trichloro*-2-*nitropropane* was removed in steam and extracted from the distillate with ether. When distilled under reduced pressure, it was obtained as a colourless oil (15 g.), b. p. 78—80°/12 mm. (Found: Cl, 55·3. $C_3H_4O_2NCl_3$ requires Cl, 55·3%).

1 : 2-*Dichloro*-1-*nitro*cyclo*hexane*.—A mixture of 2-chloro*cyclo*hexanone (66·25 g.) and a saturated solution of hydroxylamine sulphate (41 g.) was mechanically stirred and cooled while potassium carbonate (34·5 g.), dissolved in water (150 c.c.), was gradually added at such a rate that the temperature did not exceed 0° (compare Scholl and Matthaiopoulos, *Ber.*, 1896, **29**, 1550). The whole was then allowed to reach room temperature and stirring was continued for 3 hours. The *oxime*, which separated as a thick syrup, was extracted with ether, and the extract was washed with water and dried. After removal of the ether under reduced pressure at 25°, the residue (Found: Cl, 22·6. $C_6H_{10}ONCl$ requires Cl, 24·1%) was used without further treatment for the next operation. An attempt to distil a sample under reduced pressure resulted in violent decomposition. When chlorine was passed for 2 hours through a solution of the oxime (50·3 g.) in concentrated hydrochloric acid (100 c.c.), cooled to 0° (compare Piloty and Steinbock, *Ber.*, 1902, **35**, 3101), 1 : 2-*dichloro*-1-*nitroso*cyclo*hexane* separated as a deep blue oil. Owing to the instability of this type of compound, the product was washed with cold water and the main part oxidised without delay, but a specimen was dried (Na_2SO_4) and analysed (Found: Cl, 38·8. $C_6H_9ONCl_2$ requires Cl, 39·0%). The nitroso-compound was gradually added, with shaking, to a mixture of nitric acid (43 c.c., *d* 1·42) and glacial acetic acid (105 c.c.) which was maintained at 80° (compare Rheinboldt and Dewald, *Annalen*, 1927, **455**, 300). After the whole had been poured into water (750 c.c.), the product was extracted with ether and washed with dilute aqueous sodium hydroxide. When the extract was dried and fractionated, 1 : 2-*dichloro*-1-*nitro*cyclo*hexane* was collected in good yield as a pale yellow oil, b. p. 130°/35 mm. (Found: C, 37·2; H, 4·5; Cl, 35·3. $C_6H_9O_2NCl_2$ requires C, 36·4; H, 4·5; Cl, 35·9%). This substance, which might consist of geometrically isomeric forms, almost completely solidified at room temperature, but became liquid again on being heated to 41°.

1 : 2-*Dichloro*-2-*nitropropane*.—(a) Chlorine was passed through a suspension of the sodium salt of 2-nitro-*n*-propyl alcohol (67 g., Earl, Ellsworth, Jones, and Kenner, *J.*, 1928, 2697) in dry ether (300 c.c.), the whole being cooled in ice and mechanically stirred. The course of the reaction was followed by stopping the stream of chlorine from time to time and testing the solution with starch–potassium iodide paper after a few minutes of continued stirring. When the chlorination was completed, the sodium chloride was filtered off and washed with a little ether. After the solvent had been removed from the united ethereal solutions, the residue was distilled, and 2-chloro-2-nitro-*n*-propyl alcohol (60 g.) collected at 82—89°/10 mm. (Found: Cl, 25·6. Calc. for $C_3H_6O_3NCl$: Cl, 25·4%). It solidified

at room temperature but was liquid again at 27° (compare Henry, *Rec. Trav. chim.*, 1897, **16**, 193; also Wilkendorf and Trénel, *Ber.*, 1924, **57**, 306). When treated with phosphorus pentachloride under conditions similar to those described for 1 : 2 : 3-trichloro-2-nitropropane, the hydroxy-compound gave 1 : 2-*dichloro*-2-*nitropropane* as a colourless oil, b. p. 76—78°/33 mm. (Found : Cl, 44·3. $C_3H_5O_2NCl_2$ requires Cl, 44·9%).

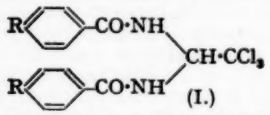
(b) The blue oil which separated when chlorine was passed through a solution of the oxime of chloroacetone in concentrated hydrochloric acid, cooled in ice, was immediately oxidised under conditions similar to those used for 1 : 2-dichloro-1-nitroso*cyclo*hexane. 1 : 2-Dichloro-2-nitropropane was obtained as an almost colourless oil, b. p. 77—78°/34 mm. (Found : C, 22·3; H, 3·2; N, 9·1; Cl, 44·2. $C_3H_5O_2NCl_2$ requires C, 22·8; H, 3·2; N, 8·9; Cl, 44·9%). The yield was 46% of the theoretical.

We are indebted to Sir Robert Robinson for his interest in these investigations, and to the Chief Scientist, Ministry of Supply, for permission to publish the work.—Dyson Perrins Laboratory, Oxford University. [*Received, February 20th*, 1948.]

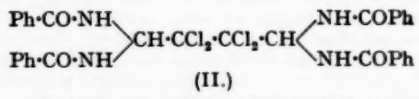
The Condensation of Chloral with Aryl Cyanides. By R. F. Batt and D. Woodcock.

The reaction between phenyl cyanide and chloral has been investigated by several workers. Thus Hepp and Spiess (*Ber.*, 1876, **9**, 1424) obtained a compound, m. p. 257°, from the exothermic reaction which took place in the presence of sulphuric acid. Pinner and Klein (*Ber.*, 1878, **11**, 10) obtained an impure product by using gaseous hydrogen chloride, whilst Béhal and Choay's product, m. p. 267° (*Ann. Chim.*, 1892, **26**, 33), was prepared from chloralimide and benzoyl chloride.

During the preparation of D.D.T. analogues by Wain (*Ann. Rept. Res. Sta. Long Ashton*, 1944, 126) attempts to prepare the *pp'*-dicyano-derivative by the Baeyer condensation (*Ber.*, 1872, **5**, 25, 280, 1094) with phenyl cyanide led to a product, m. p. 272—273° (decomp.), which decomposed on attempted dehydrochlorination with alcoholic potassium hydroxide. It has now been shown that this compound is identical with that produced by the earlier workers, and the formula (I; R = H) assigned to it by



(I.)



(II.)

Hepp and Spiess (*loc. cit.*) has been confirmed by its synthesis from benzamide and chloral.

Analogous compounds (I; R = Cl and R = Me) have been prepared from *p*-chlorophenyl cyanide and *p*-tolyl cyanide.

Reduction of (I; R = H) with zinc dust in alcoholic solution gave a product which probably possesses the bimolecular structure (II).

1 : 1 : 1-*Trichloro*-2 : 2-*dibenzamidoethane* (I; R = H).—(*a*) (cf. Wain, *loc. cit.*). Phenyl cyanide (10·2 g.) and freshly distilled chloral (7·4 g. ≡ 0·5 mol.) were stirred during the addition of concentrated sulphuric acid (5 c.c.) and oleum (1—2 c.c.). The colour became a deep yellow, and the whole set to a vitreous mass which crystallised from a large amount of glacial acetic acid in a mass of felted needles (6·9 g.), m. p. 265—266° (decomp.).

(*b*) Benzamide (2·4 g.) and chloral (1 c.c. ≡ 0·5 mol.) were heated in an oil-bath at 150—160° for 3 hours. The solid obtained on cooling crystallised from acetone–benzene (1 : 1) in colourless needles (2·5 g.), m. p. 264° (decomp.) undepressed by admixture with the product from (*a*) above or with Wain's product (Found : C, 51·6; H, 3·5; N, 7·3; Cl, 28·5. Calc. for $C_{16}H_{13}O_2N_2Cl_3$: C, 51·7; H, 3·5; N, 7·5; Cl, 28·6%).

Hydrolysis with 70% sulphuric acid gave benzoic acid, chloral, and ammonia, but no benzamide could be obtained by using 2N-acid (cf. Hepp and Spiess, *loc. cit.*).

2 : 2 : 3 : 3-*Tetrachloro*-1 : 1 : 4 : 4-*tetrabenzamidobutane* (II).—The compound (I; R = H) (2·0 g.) was refluxed with ethyl alcohol (30 c.c.), zinc dust (4 g.) and concentrated hydrochloric acid (5 c.c.) for 0·5 hour, the excess alcohol distilled off, and the residual syrup extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and the solvent removed. The residue crystallised from ethyl alcohol in rosettes of tiny prisms (0·9 g.), m. p. 200—201° (decomp.) [Found : C, 56·4; H, 4·4; N, 8·5; Cl, 20·3; *M* (Rast), 622, 645. $C_{32}H_{24}O_4N_4Cl_4$ requires C, 57·2; H, 3·9; N, 8·3; Cl, 21·1%; *M*, 672]. The m. p. of this product was undepressed by admixture with a substance, m. p. 196—197°, isolated by Wain (unpub.) from the product of a phenyl cyanide–chloral condensation which was left for several weeks before being examined.

1 : 1 : 1-*Trichloro*-2 : 2-*di*-p-*toluamidoethane* (I; R = Me).—*p*-Tolyl cyanide (11·7 g.) and freshly distilled chloral (7·3 g. ≡ 0·5 mol.) were warmed together until homogeneous and then stirred during the dropwise addition of oleum (2 c.c.). The ensuing exothermic reaction gave a viscous dark brown liquid which crystallised from glacial acetic acid in rosettes of prisms (7·9 g.), m. p. 237—238°, raised to 248° by recrystallisation from the same solvent [Found : C, 53·7; H, 4·4; N, 6·7; Cl, 26·0; *M* (Rast), 376, 390. $C_{18}H_{17}O_2N_2Cl_3$ requires C, 54·1; H, 4·3; N, 7·0; Cl, 26·6%; *M*, 399·4]. Hydrolysis with 70% sulphuric acid yielded *p*-toluic acid as well as chloral and ammonia.

1 : 1 : 1-*Trichloro*-2 : 2-*di*-p-*chlorobenzamidoethane* (I; R = Cl).—*p*-Chlorophenyl cyanide (13·7 g.) and chloral (7·3 g. ≡ 0·5 mol.) were treated as in the previous experiment. Crystallisation of the product from glacial acetic acid gave rosettes of prisms, m. p. 274—275° (decomp.) [Found : C, 44·0; H, 2·7; N, 5·7; Cl, 38·0; *M* (Rast), 410, 421. $C_{16}H_{11}O_2N_2Cl_5$ requires C, 43·6; H, 2·5; N, 6·3; Cl, 40·3%; *M*, 440·3]. Ammonia, chloral, and *p*-chlorobenzoic acid were obtained on hydrolysis.—University of Bristol, Department of Agriculture and Horticulture, Research Station, Long Ashton, Bristol. [*Received, February 27th*, 1948.]

OBITUARY NOTICE.

FREDERICK MAURICE ROWE.*

1891—1946

FREDERICK MAURICE ROWE, Professor in the Department of Colour Chemistry and Dyeing at the University of Leeds, died on December 8th, 1946, at the age of fifty-five. He was born on February 11th, 1891, at Stroud in Gloucestershire where his father, H. J. Rowe, was engaged in business as a coal merchant and dealer in builders' materials, under the name of Wood and Rowe. From 1901 to 1908 he attended Marling School, Stroud, and always retained for it a strong attachment for which there were solid grounds. The school, founded and endowed in 1887 by Sir Samuel Marling, a prominent figure in the West of England cloth trade in that part of Gloucestershire, had attracted the attention of the Worshipful Company of Clothworkers by whose efforts a Department of Dyeing had been established at the Yorkshire College, Leeds. The Company decided to provide funds for an annual leaving scholarship to help a Marling School boy to proceed to Leeds for two years' technological training in textile dyeing at the College. Similar provision was made at Cheltenham Grammar School, and in consequence there were unusual opportunities for boys from Gloucestershire to go north for scientific and technical training whilst becoming familiar with another district famous for its woollen industry. On his mother's side Rowe was descended from a family of Huguenots who fled from France after the revocation of the Edict of Nantes in 1685 and settled in Gloucestershire to practise their craft of woollen manufacture with which some members of the family continued to maintain a connexion. This circumstance and the Cotswold environment may have helped to direct Rowe's choice of a career, but a love for chemistry was awakened in him by one of the masters at the school, Bartlett, whose influence in after years he frequently acknowledged with gratitude. The first holder of the Clothworkers' Scholarship for Marling School was R. J. Steele, who became a textile chemicals manufacturer in Bradford. A personal friendship between Steele's parents and Rowe's undoubtedly contributed to the result that in 1905 Rowe decided to work for the scholarship which would take him to Leeds, and three years later he duly became the sixth Marling Clothworkers' scholar, although he had at one time been described as the laziest boy in the school. It is hard to believe, however, that as a boy Rowe was ever consistently lazy, for the boy is father to the man, and the man was possessed of amazing industry. At school he distinguished himself at both work and games, and showed the personality of a leader by becoming Head Prefect.

Coming to Leeds as a young man of seventeen, a stranger in a strange place, Rowe at once found himself called on to make a major decision. The Yorkshire College had in 1904 become the University of Leeds, and a course had been established in Colour Chemistry and Dyeing, leading to a B.Sc. degree with Honours. This course, however, required three years, whilst the Marling Scholarship provided for two years only, and the holder had always been expected to follow a shorter course of study leading to a Diploma in Dyeing. Rowe's parents had kept him at Marling School at a considerable sacrifice and could not be called on for further help, but, nevertheless, he decided that the diploma was not good enough for him and that he must take the degree course, gambling on getting his scholarship renewed for a third year. The fight was a hard one, but in the end Rowe got his third year and made it secure for every Marling boy who subsequently went to Leeds.

Rowe spent five years at Leeds University where he acquitted himself with distinction, graduating with First Class Honours in 1911 and becoming President of the Union, besides receiving the Le Blanc medal and the award of a Clothworkers' Research Scholarship. This scholarship enabled him to start work under A. G. Green, then Professor in the Department and in the full tide of his researches on dyestuffs. At the end of a year's research Rowe gained his M.Sc. degree and a Clothworkers' Research Fellowship, but in the following year he decided to take an industrial research post with Messrs. Joseph Crosfield & Sons Ltd., the soap manufacturers of Warrington. This excursion into industry proved to be but a brief interlude in an academic career, although it had some importance for Rowe in that it provided him with an opportunity to spend a short time under Professor Freundlich in Brunswick studying colloid chemistry, and also gave him some acquaintance with manufacturing processes and with the properties of soap.

The ferment of war, however, brought Rowe finally back in 1916 to teaching and to dyestuffs. A. G. Green had gone from Leeds to Manchester where he was directing a Dyestuffs

* Reprinted by permission from *Obituary Notices of Fellows of the Royal Society*, Vol. 6.

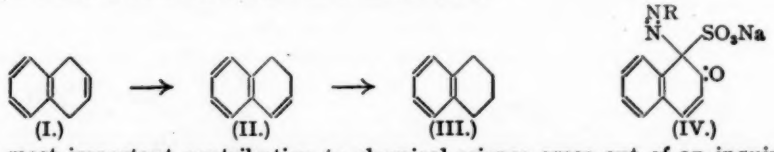
Research Laboratory at the College of Technology and at the same time assisting the firm of Levinstein Ltd. to extend its range of dye manufacture. Rowe became assistant to Green and lecturer in dyestuffs, and, two years later when Green severed his connexion with the College, head of the laboratory. During the following eight years Rowe laid the foundations of his researches and of his unique knowledge of dyes. In 1926 he was appointed Reader in Tinctorial Chemistry and Dyeing in succession to Dr. Edmund Knecht, but the same year there came to him the opportunity for which he had waited and hoped almost from the day he went to Leeds as a raw schoolboy. The retirement of A. G. Perkin created a vacancy in the Department of Colour Chemistry and Dyeing at Leeds, and Rowe had already made for himself such a position that he was the obvious choice for the Chair, which he held until his death.

Rowe's life pursued a steady, placid course, marked by no violent changes or experiences, but occupied to the full with teaching, research, and service. He never seemed to have an idle moment. A tall man, of unusually handsome, commanding appearance, he inspired respect and confidence. To him his profession was a true vocation, a calling to which his life was devoted. Combined with a stern sense of duty and service he had a bull-dog persistence which gripped a problem until some sense had been worried out of it. This characteristic may have restricted the range of topics on which he concentrated in research, but these, once started, were pursued with great determination. Lacking the brilliance of some of his chemical contemporaries, he was second to none in the thoroughness with which his work was planned and the care with which it was executed and checked. He always had time for work, and during his last illness complained in a letter that he could no longer put in his customary sixteen hours a day. One of Rowe's lovable characteristics was his solicitude for his students. His department at Leeds was comparatively small, with an intake of about ten students each year. Rowe made it his business to know them all personally, to invite them to his house, and to learn their family and financial circumstances. The department was in fact, under Rowe, almost a family affair. He had a specially warm place in his heart for the scholars from Gloucestershire for whom he and Mrs. Rowe held a special party each year. He regarded it as his duty to the students and to the College to ensure that every one of them eventually found a suitable post, and in this he never failed. It was a tribute to his department's reputation, built up by his predecessors and maintained for twenty years by Rowe himself, that the demand for its students always exceeded the supply. The students were suited, as Rowe was proud of boasting, not only for posts with dyers or dye manufacturers, but for positions having nothing to do with colour, where the principal requisite was a sound scientific training. By his constant research activities in both pure and applied chemistry Rowe kept the attention of his students fixed on the importance of the experimental method and the inquiring mind for the advance of the technology for the practice of which they were training.

Those who knew Rowe's attitude to science best soon came to recognise that, although he was engaged all his life in the teaching and study of a technological subject, pure organic chemistry had an irresistible attraction for him and that he turned for preference to organic chemistry for research topics. He had a passion for the accumulation of facts and would spare no pains to verify them, leaving broad generalisations and theoretical speculations to others. Nevertheless, he recognised that the scientific development and appreciation of the technology of dyestuffs, their properties and application, could not be accomplished solely by the methods of organic chemistry, but required the application of physics and physical chemistry in increasing measure. In the Department of Textile Industries at Leeds, under the influence of Speakman, an important research school was growing up, and during the last fifteen years of his life Rowe joined with Speakman in researches demanding contributions from both the physical and the chemical side. During this period Rowe benefited much, on his own admission, from close contact with the Dyestuffs Division of Imperial Chemical Industries Limited, for whom he acted as consultant, serving for many years on a technological panel. This association with industry brought to his attention several problems which he attacked with his customary zeal.

Rowe's first researches were carried out in collaboration with A. G. Green at Leeds, arising out of Green's investigations of the constitution of stilbene dyes. They have been summarised by J. Baddiley in his admirable obituary notice of Professor Green and, since Rowe did not return to the subject, require no further mention here. On rejoining Green in Manchester he started work on the chemistry of tetralin derivatives with the ultimate object of determining whether *ar*-tetrahydro-α-naphthylamine and *ar*-tetrahydro-α-naphthol would have any value as dyestuff intermediates. Most of this work was done before the appearance in 1922 of Schroeter's comprehensive paper on tetralin. In the course of experiments on the reduction of α-naphthylamine by boiling it with sodium in presence of an alcohol, *ar*-tetrahydro-α-naphthylamine was produced only when the alcohol used was amyl, none when butyl or ethyl

alcohol was used. Bamberger had made a similar observation when reducing naphthalene itself, finding that with ethyl alcohol dihydro-, and with amyl alcohol tetrahydro-naphthalene was formed. The prevailing view that temperature was the factor deciding how far reduction would proceed was disproved by Rowe by a series of careful experiments. He showed that the first reduction product of naphthalene by sodium and an alcohol is 1 : 4-dihydronaphthalene (I) which cannot be reduced further by sodium and any alcohol. When, however, this is heated with sodium alkoxide it is converted, at a rate increasing with the temperature and with the concentration of sodium alkoxide, into the isomeric 1 : 2-dihydronaphthalene (II), which can then be reduced further to tetrahydronaphthalene (III). When amyl alcohol is used, conditions favour the conversion of (I) into (II), and the reaction proceeds to the tetrahydro-stage. By an elegant series of experiments the same course was shown to be followed in the reduction of α-naphthylamine. The first reduction product was a dihydro-compound which gave (I) when the amino-group was removed and, therefore, must be 5 : 8-dihydro-1-naphthylamine. By prolonged boiling with sodium ethoxide this was converted into an isomeric compound which by elimination of the amino-group gave (II) and hence was either 5 : 6- or 7 : 8-dihydro-1-naphthylamine. The last compound, it was shown, could be reduced to 5 : 6 : 7 : 8-tetrahydro-1-naphthylamine even by sodium and ethyl alcohol, amyl alcohol not being required once the isomerisation had taken place (*J. Soc. Chem. Ind.*, 1920, **39**, 241T; Rowe and Levin, *J.*, 1920, **117**, 1574). Later it was shown that similar considerations applied to the reduction of α-naphthol, and the dihydro-α-naphthols obtained by reduction and isomerisation were identified by their preparation from the corresponding dihydro-α-naphthylamines (*J.*, 1921, **119**, 2021). With J. S. H. Davies, Rowe made a further study of the bromination and oxidation of 5 : 8-dihydro-1-naphthylamine (*J.*, 1922, **121**, 1000) and eventually published a description of a large number of azo-dyes in which *ar*-tetrahydro-α-naphthylamine and its 4-nitro- and 4-sulpho-derivatives had been used as components. Compared with corresponding dyes containing α-naphthylamine they were generally less deep in shade and showed no technical advantage (*J. Soc. Dyers and Col.*, 1925, **41**, 5).

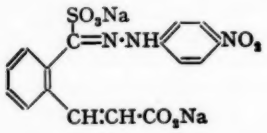


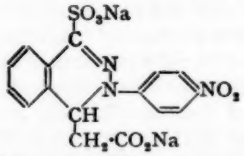
(I.) (II.) (III.) (IV.)

Rowe's most important contribution to chemical science arose out of an inquiry into the anomalous behaviour of β-naphthol-1-sulphonic acid with certain types of diazo-compound, resulting, as he discovered, in an unusual fission of the naphthalene ring followed by cyclisation with formation of heterocyclic ring systems. As early as 1918 he had studied the course of the reaction between β-naphthol-1-sulphonic acid and diazotised aromatic amines. The first product is a diazonium sulphonate which on treatment with a molecular proportion of sodium carbonate undergoes isomerisation to form the sodium salt of a derivative of β-naphthaquinone (IV). This, on treatment with acid, forms a true azo-compound of β-naphthol, with elimination of the sulphonic group. In this way, as Grant Hepburn showed, the well-known Para Red could be obtained from β-naphthol-1-sulphonic acid and diazotised *p*-nitroaniline. Interest in the reaction was intensified, however, by an observation by Grant Hepburn, made about 1921, that when the *p*-nitrobenzenediazonium β-naphthol-1-sulphonate was treated with excess of alkali an intense transient crimson colour appeared, and subsequent acidification produced only a trace of Para Red but a high yield of a new homogeneous yellow compound. At Grant Hepburn's request Rowe took up the study of this reaction, which led him into new chemical territory, the exploration of which occupied his attention for many years, indeed, until the end of his life.

It was soon established that the new reaction only occurred when the diazonium compound used contained a strongly negative substituent, generally a nitro-group. Attention was at first concentrated on the compound from *p*-nitrodiazobenzene, from which many degradation products were obtained and analysed by Miss E. Levin, who was Rowe's able assistant at this time, but for long the nature of the chemical changes which were occurring eluded the investigators. At length, however, one of the degradation products gave by oxidation with chromic acid two identifiable products, phthalimide and benzoquinone, and it at once became clear that fission of the naphthalene ring had occurred and a new ring system had been set up from which eventually had been obtained *p*-aminophenylphthalimidine, the compound which by oxidation had given phthalimide and benzoquinone. From the analyses of the intermediate compounds it was not difficult to construct the whole story which was published in 1926 (*J.*,

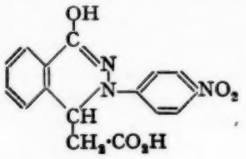
1926, 690). Subsequent work with other diazo-compounds confirmed the original conclusions, only a few minor modifications of the formulæ first suggested for some of the products having to be made.

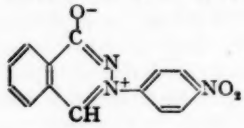
(V.) 

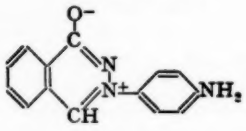
 (VI.)

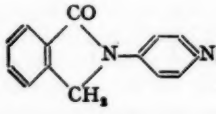
The first action of excess of alkali on the quinone sulphonate (IV) is to cause fission of the naphthalene ring between C^1 and C^2 with formation of a phenylacrylic acid derivative (V), which is responsible for the intense colour, but this quickly changes by cyclisation to the phthalazine derivative (VI). Compound (V) was at first hypothetical, but some years later the corresponding *o*-nitro-compound was isolated and characterised, being obtained from sodium 1-(*o*-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate (Rowe *et al.*, *J.*, 1935, 1796).

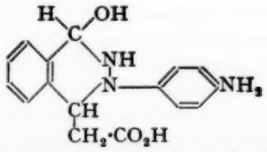
From compound (VI) a bewildering family of new compounds was obtained, only a few of which can be noted here. The sulphonic acid group was removed by boiling the compound with hydrochloric acid; sulphur dioxide was evolved and the hydroxy-compound (VII) was formed. This by boiling with 50% sulphuric acid lost acetic acid to give the phthalazone (VIII) which by reduction gave successively the aminophthalazone (IX) and *p*-aminophenylphthalimidine (X). Alternatively (VII) could first be reduced to the aminophenyltetrahydrophthalazine

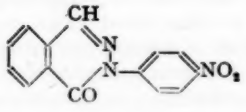
(VII.) 

 (VIII.)

(IX.) 

 (X.)

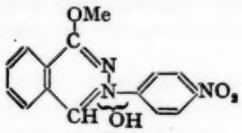
(XI.) 

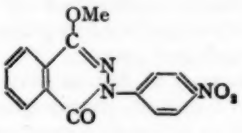
 (XII.)

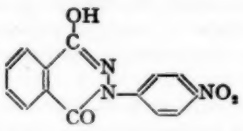
(XI) which on boiling with mineral acid gave (IX). There was at first some doubt about the constitution of (VIII) since it might have been the isomeric 3-*p*-nitrophenylphthalaz-4-one (XII) which was, however, synthesised by an unambiguous route and found to be different. The phthalazone (VIII) could be methylated to form the methosulphate of a base, probably (XIII), which combined with ethyl alcohol to form an unstable compound which changed, on being heated, to 4-keto-1-methoxy-3-*p*-nitrophenyldihydrophthalazine (XIV), which was demethylated to (XV). This reaction was not explained, but the constitution of (XV), which is identical with 1 : 4-diketo-3-*p*-nitrophenyltetrahydrophthalazine, was confirmed by preparing it from phthalyl-*p*-nitrophenylhydrazide (XVI) by the method of Chattaway and Tesh (*J.*, 1920, 712). Since by alkylation (XV) gives (XIV) and not an *N*-methyl derivative, it was concluded that it is best represented as a hydroxy-ketone, not as a diketone (*J.*, 1935, 1808).

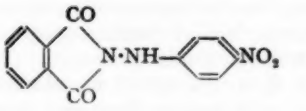
Another interesting series of compounds was obtained from compound (VII) by oxidation with cold chromic acid. With this reagent, instead of loss of acetic acid, decarboxylation occurred with formation of the 4-methyl derivative of (VIII), namely 3-*p*-nitrophenyl-4-methylphthalaz-1-one (XVII), a golden-yellow crystalline substance. This compound proved to be of considerable chemical interest. Like the phthalazone (VIII) it could be methylated to a methosulphate, but this on basification was transformed into a methylene compound (XVIII). Unlike most other known methylene bases, which are non-crystalline and unstable, this was stable and crystalline, as were corresponding compounds containing *o*-Cl, 2 : 6-Cl_2, 2 : 6-Br_2, and *o*-Me as well as the 4-NO_2 group. Their basicity is low, and of their salts only the perchlorate could be obtained pure, but they had most of the properties of other pseudo-bases. They were

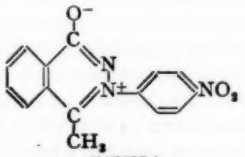
studied in much detail, and from them were prepared many methine dyes, some of which functioned as photographic desensitisers. The methylene bases are oxidised by nitrous acid and by *p*-nitrosodimethylaniline to ketones of type (XIV).

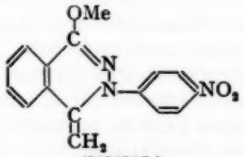
(XIII.) 

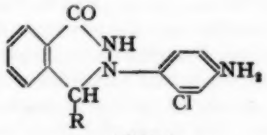
 (XIV.)

(XV.) 

 (XVI.)

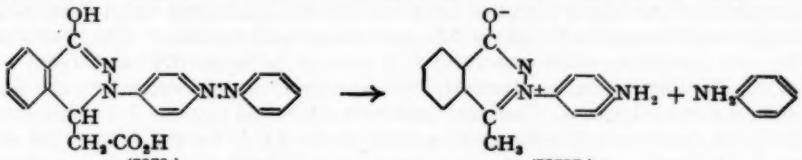

(XVII.)


(XVIII.)


(XIX.)

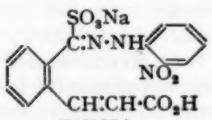
Some interesting new features were discovered when, instead of *p*-nitrodiazobenzene, other diazo-compounds were used. For instance, using *o*-chloro-*p*-nitrodiazobenzene, an intermediate reduction stage between (IX) and (X) was realised with formation of the ketotetrahydrophthalazone (XIX, R = H or Me) which was difficult to reduce to the phthalimidine.

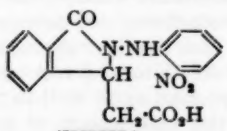
When 4-aminoazobenzene was used for diazotising and reacting with β-naphthol-1-sulphonic acid, only a small yield (19%) of the phthalazine compound could be obtained, the principal product always being benzeneazobenzeneazo-β-naphthol, but 4′-nitro-4-aminoazobenzene gave a much higher yield (63%). The benzeneazophenyl derivative (XX) and its *p*-nitro-derivative

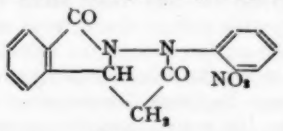

(XX.) (XXI.)

showed remarkable behaviour in that, when boiled with dilute sulphuric acid, they did not lose acetic acid, but underwent decarboxylation and simultaneous fission of the azo-group, giving (XXI) and aniline or *p*-nitroaniline. Rowe considered that the splitting of the azo-group was primarily a hydrolysis, not a reduction, since the azo-group should not be reduced in preference to the nitro-group (*J.*, 1932, 1118). It is significant, however, that in absence of the azo-group an equivalent amount of an oxidising agent is necessary to bring about the change, as in the conversion of (VII) into (XVII). The observation led Rowe later to examine carefully the behaviour of simpler azo-compounds with acids (see p. 2329).

Experiments in which *o*-nitroaniline (or its 4-chloro- or 4-methyl derivative) was used gave especially interesting results, not only because, as already mentioned, primary ring-fission


(XXII.)


(XXIII.)


(XXIV.)

products, derivatives of phenylacrylic acid, were isolated, but because alternative cyclisation products from these were discovered. The action of concentrated sodium hydroxide solution on sodium 1-*o*-nitrobenzeneazo-β-naphthaquinone-1-sulphonate is immediately to split the naphthalene ring with formation of sodium benzaldehyde-*o*-nitrophenylhydrazone-ω-sulphonate-2-β-acrylic acid (XXII). This cyclises only slowly to the phthalazine derivative, and by quick acidification followed by neutralisation with sodium carbonate it can be isolated. This compound when boiled with dilute acid is converted with loss of sulphur dioxide into the *o*-nitrophenyl-

hydrazide of *o*-carboxyphenylacrylic acid which is cyclised by heat or boiling sodium carbonate solution into a new ring compound, 2-(*o*-nitrophenylamino)*iso*indolinone-3-acetic acid (XXIII). This again undergoes further cyclisation when boiled with acetic anhydride to (XXIV) which is, however, readily hydrolysed by acids back to (XXIII). Still another ring-closure was achieved by reducing the nitro-group (XXIV), the resulting amino-group condensing with the neighbouring carbonyl group.

There is no need to discuss every paper in the series, which appeared under the title " A new reaction of certain diazosulphonates derived from β-naphthol-1-sulphonic acid ", but reference must be made to a posthumous paper with A. T. Peters in which it is shown that, in spite of what was said in the first paper, phthalazine formation can be brought about from 1-benzeneazo-β-naphthaquinone-1-sulphonate; in other words a strongly negative group in the amine used for diazotisation is not necessary, but the reaction must be carried out under carefully controlled conditions.

Although Rowe published in collaboration with his students and staff a number of other researches in pure organic chemistry, none had the sustained interest or the novelty of that just described. They had the common factor that they concerned substances, aromatic in character, of possible interest as dyestuff components, as exemplified by papers on *tert.*-butylanthraquinone, *tert.*-butylnaphthalenes, benzoylacenaphthene, and derivatives of tetrachlorobenzene.

Rowe's technological work was concentrated for a long period on azo-dyes, particularly the group of insoluble colouring matters used as pigments or as dyes when produced on the fibre. He developed their analysis and identification to a high degree, and devoted much time to the study of their behaviour on the fibre under conditions to which they were likely to be subjected in practice. Such dyes, frequently called " azoic " dyes, are obtained by coupling a diazotised aromatic amine with β-naphthol or with the anilide or a substituted anilide of 2-hydroxy-3-naphthoic acid. Products for the formation of these colouring matters in dyeing and printing processes were being brought on to the market under trade names by German firms in the years following 1918, and Rowe made it his business to discover all he could about them. He rendered service to the industry by publishing the constitutions of many of the bases and Naphtols (the generic name for arylamides of 2-hydroxy-3-naphthoic acid), and, to assist others to identify the bases, published a table giving the melting point, crystalline form, and colour reactions of azo-dyes obtained by coupling the diazotised bases with β-naphthol and 2 : 3-hydroxynaphthoanilide (Naphtol AS) (see Rowe and Levin, *J. Soc. Dyers and Col.*, 1924, **40**, 220, and numerous other papers in this journal between 1921 and 1930). Rowe's knowledge in this field fitted him particularly for the task of expert witness in the important patent action brought by Imperial Chemical Industries Limited against I.G. Farbenindustrie in 1930. The patent action in question was a petition by I.C.I. for the revocation of certain patents granted to the I.G. on grounds of priority of publication, common knowledge, and insufficiency of description. At a much earlier date, during 1912—1914, Chem. Fab. Griesheim-Elektron had patented the manufacture and use of a wide range of arylamides of 2 : 3-hydroxynaphthoic acid, for the preparation of azo-dyes as pigments or on the fibre; much later the I.G. had obtained the patents now petitioned against, covering certain selected members of the same group of compounds, on the grounds that these selected members had peculiar advantages in giving specially fast dyes, notably fast to keir boiling. (Keir boiling is a process in which cotton goods, frequently already printed with a coloured pattern, are boiled with dilute caustic soda solution to bleach the white cotton; the colouring matter should be as nearly as possible unaffected.) Rowe's task in this case was to test experimentally the defendants' claim, which he did by preparing some hundreds of samples of cotton dyed with colouring matters made from the intermediates claimed in the later patents and comparing them with others made from other intermediates not amongst the selected ones, but covered by the earlier patents. The Germans had not specified any particular test to justify their claims for the selected compounds, and Rowe used a test which had been recommended by a German Fastness Commission. Rowe showed such skill in putting his experimental findings before the court, and in pointing out the inadequacy of experimental tests put forward in evidence by the defendants, that the judge was convinced beyond a shadow of doubt that the special claims of the patents in dispute were unwarranted, and they were, in fact, revoked. This case is of special importance in regard to future chemical patents since, in the course of his judgment, Mr. Justice Maugham defined for the first time the requirements of a valid selection patent.

Characteristically, Rowe was not content with the empirical experiments which the patent case had necessitated, but went on to inquire more deeply into the changes taking place with dyes which were not fast to the keir-boiling test. He had already published some results

having a bearing on the problem, in which he had shown that boiling soap solution causes insoluble azo-dyes on cotton to aggregate into coarse, crystalline particles visible under the microscope, some of the dye being removed entirely from the fibre. This aggregation produces a change not only in the depth of the dyeing, but also in its hue and fastness to light and rubbing, besides causing dyed viscose to lose lustre (*J. Soc. Dyers and Col.*, 1926, **42**, 207; 1929, **45**, 67). In the keir-boiling test, which is a prolonged boil with 0·36% aqueous caustic soda, not only can this physical transformation occur, but also hydrolysis of an amide group and reduction brought about by the cellulose. Reduction may occur at the azo-group, and nitro-groups, if present, are usually affected so that no dye containing this group stands up to the keir-boiling test. The exact course of these chemical changes is affected by the constitution of the dye, especially by the orientation of nitro-groups, and much careful quantitative work was done in which decomposition products were isolated and identified (*ibid.*, 1931, **47**, 29; Rowe and Ueno, *ibid.*, 1931, **47**, 35; Rowe and Jowett, *ibid.*, 1931, **47**, 163; Rowe and Giles, *ibid.*, 1935, **51**, 314).

Rowe also started an investigation of the decomposition of azo-dyes by hot aqueous sulphuric acid, having been led thereto by the curious behaviour of some phthalazine compounds containing the benzeneazophenyl group as a substituent (see p. 2327). Several types of azo-compound were found to undergo fission at the azo-group with regeneration of the amine originally used as the diazo-component, but the other fission product could not be identified and the mechanism remains obscure. That the reaction is complex is shown by the observation that Orange I gives some α-naphthaquinone and Orange II some hydroxy-α-naphthaquinone (Rowe and Dangerfield, *J. Soc. Dyers and Col.*, 1936, **52**, 48).

During the later years of his life Rowe became more and more convinced, through his industrial contacts, of the importance of investigating technological phenomena and processes from the scientific point of view, and that such studies were suitable and proper for the Technological Department of a University. He would have proceeding at the same time in his laboratories chemical studies of new products made available by industry, such as *m*-5-xylenol or 1 : 2 : 4 : 5-tetrachlorobenzene, and technological studies such as that of a new process for stripping dyes from a fibre involving the use of a higher aliphatic ammonium compound (Rowe and Glyn Owen, *J. Soc. Dyers and Col.*, 1936, **52**, 205). He investigated the phenomenon of the fading of dyeings of certain dyes on acetate rayon when exposed to burnt gas fumes. The dyes affected are aminoanthraquinones and strong evidence was found that the fading is due to the presence in the burnt gas fumes of oxides of nitrogen which react chemically with primary and secondary amino-groups.

In 1935 he commenced in conjunction with Speakman a series of researches on the dyeing of wool in which the techniques which Speakman had developed for the experimental study of keratin fibres, and Rowe's flair for painstaking chemical work, were happily blended. With the help of E. Race they developed a major inquiry into the phenomenon of unlevel dyeing of wool. It was known that exposure of wool to light and air affected its dyeing properties, this fact being shown, for instance, when a wool hair is found to be dyed more heavily at the tip end than at the root end. A consistent explanation of the observed facts was found in the assumption that exposure of wool leads to a partial breakdown of the disulphide bonds between the protein chains, resulting in changes in both its physical and chemical properties. Exposed fibre swells to a greater extent in water than the unexposed and consequently becomes more accessible to dye molecules. When the latter are colloidal they are fixed permanently in the fibre, and consequently tips of the wool staple are more heavily dyed than the root end; when they are crystalloid they first dye the tip more heavily, but can escape more readily from the more swollen end in the levelling process and eventually become more concentrated in the roots; consequently, crystalloid dyes colour the roots more heavily than the tips. Chemically, exposed fibres or parts of a fibre contain reducing groups, such as aldehyde and sulphhydryl groups, which have a reducing action on dichromate; consequently, exposed wool fixes more tervalent chromium than unexposed wool, and the shade of an after-chromed dye is affected by this difference. These findings were confirmed by a number of ingenious experiments, whilst on them were based devices by which the tips and roots could be dyed a level shade. Acid dyes can be caused to dye level shades by adjusting the degree of dispersion of the dye by suitable additions to the dye bath. Alternatively, if the fibre is treated with chromium acetate, the chromium makes new linkages between the peptide chains in place of the disrupted disulphide linkages, and the swelling power of the exposed wool is reduced and its dyeing properties brought to approximate equality with those of unexposed wool (*J. Soc. Dyers and Col.*, 1938, **54**, 141, 159). Although this treatment with chromium acetate is carried out in presence of acetic acid, the most effective salt to use is a basic acetate in which the molecular ratio of acetate to chromium is 2 : 1, and which has been aged. Many different forms of

chromium acetate were investigated, and an analytical method was devised for characterising them (*J. Soc. Dyers and Col.*, 1939, **55**, 69).

One of the last pieces of work started by Rowe was an investigation of the process of dyeing cotton, especially for heavy military equipment, in khaki colour by means of a mixture of chromium and iron oxides. One cannot imagine Rowe undertaking such a piece of inorganic research had he not regarded it as part of his contribution to the war effort. The work, carried out in association with Speakman and Race, involved a thorough investigation of the properties of the so-called iron and chromium chromates and their behaviour with water, of the composition of the pigment formed when a mixture of iron and chromium salts is treated with alkali or a chromate, and especially of the effect of the mineral deposit on the strength of the cotton. Finally a method was invented for rendering the cloth immune to fungus attack by causing some copper carbonate to be precipitated along with the khaki pigment. The results of this work have been published (*J. Soc. Dyers and Col.*, 1941, **57**, 213, 257; 1942, **58**, 32, 161; 1945, **61**, 224, 233, 310; 1046, **62**, 9, 19).

Apart from his scientific papers Rowe's literary output was not great. He translated Reinthaler's " Die Kunstseide und andere seidenglänzende Fasern " under the title " Artificial Silk ". Amongst several reviews of the different aspects of dye chemistry his most useful contribution was " The development of the chemistry of synthetic dyes, 1856—1938 ", presented in the form of lectures to the Institute of Chemistry and published by that body. It forms a very useful compact text-book of the chemistry of dyes. His Perkin centenary lecture (" The Life and Work of Sir William Henry Perkin ") and obituary notice of Arthur George Perkin, both for the Society of Dyers and Colourists, are sympathetic accounts of father and son both famous in dyestuff history.

During all his working life Rowe was closely associated with the Society of Dyers and Colourists, of which he became a member in 1917. Of his many services to the Society the most important was undoubtedly the editorship and production in 1924 of the " Colour Index " and the Supplement thereto in 1928. Before the publication of this work, those concerned with commercial dyestuffs had to rely for collected information on the German work, Schulz's " Farbstofftabellen ". A book of reference in English was badly needed, apart from the fact that the changes in the dyestuff industry resulting from the war of 1914—1918, and the rapid expansion of the range of dyestuffs had put Schulz entirely out of date. The collection and verification of the mass of data included in the " Colour Index " was an amazing feat of industry and patience; as an example of the care he took, he personally checked every patent reference. Rowe served on the Publication Committee of the Society from 1922 to 1946, and was joint editor of its *Journal* from 1933 to 1942, and editor from 1942 until his death. Rowe's temperament was particularly fitted for editorial work; indeed his colleagues well knew that his first reaction to any report or document was more likely to be that of the critical editor than the scientist. He maintained the standard of the *Journal* at a very high level, and his production of the special Jubilee number in 1934 was particularly successful. He served on the Council of the Society from 1924 to 1929, in which year he became a Vice-President, and in 1944 the Society paid him the honour of making him an Honorary Member. He joined the Chemical Society in 1918 and served on its Council from 1931 to 1934. He became a Fellow of the Institute of Chemistry in 1921, the same year in which the University of Leeds granted him the degree of D. Sc. Besides receiving four times the award of the Dyers' Company's Medal for the best paper of the year in the *Journal of the Society of Dyers and Colourists*, he was presented with the Society's Gold Medal in 1934 for his services. In 1932 he became a Liveryman of the Worshipful Company of Dyers, and in 1944 received the honorary Freedom and Livery of the Worshipful Company of Clothworkers.

His election to the Fellowship of the Royal Society in 1945 gave him the greatest satisfaction, especially so because his life was already overclouded by illness which was restricting his activity. He did indeed manage to go to London to be admitted to the Royal Society in May 1945, the last considerable journey he made. For the last three years of his life Rowe put up a truly heroic struggle against an affection of the kidneys involving growing disability, intense physical discomfort, and susceptibility to all kinds of minor ailments. His health had probably suffered because, out of an intense spirit of patriotism, he had in 1940 taken a commission in the Home Guard, thereby involving himself in night military exercises in addition to his already heavy daily duties. He refused to give in and undoubtedly prolonged his own life by applying his scientific knowledge to the treatment of his condition. Almost to the last he worked to write up an account of his researches whilst time remained. He loved life for what he could give to it, not for what he could take, and when he could no longer give he laid it down.

He married, in 1916, Mary Nield Cockburn, youngest daughter of Sir George and Lady Cockburn of Leeds, who survives him.

E. H. Rodd.

TEEPOL - for simplified and improved processing . . .

TEEPOL
neutral liquid wetting agent and detergent.

- **TEXTILES**: scouring, carbonising, anti-shrinking, bleaching, dyeing, finishing.
- **LEATHER AND FUR TRADES**: soaking, scouring, pickling, stripping, wetting-back, fat-liquoring, dyeing.
- **LAUNDRIES**: washing all classifications, especially woollens, silks, rayons, coloured goods, and all heavily soiled articles.
- **WORKS MAINTENANCE**: cleaning all types of plant and equipment in the factory, canteens, workshops.
- **PAINT MANUFACTURE**: stabilizing emulsion-based paints; wetting and dispersing pigments.
- **PAPER MAKING**: boiling and pulping straw, esparto, rags; bleaching, dyeing, sizing; cleaning wires, felts.
- **ENGINEERING**: de-greasing, acid pickling and electro-plating.

Write for Technical Information Sheets regarding the detailed applications of "TEEPOL" (Registered Trade Mark).

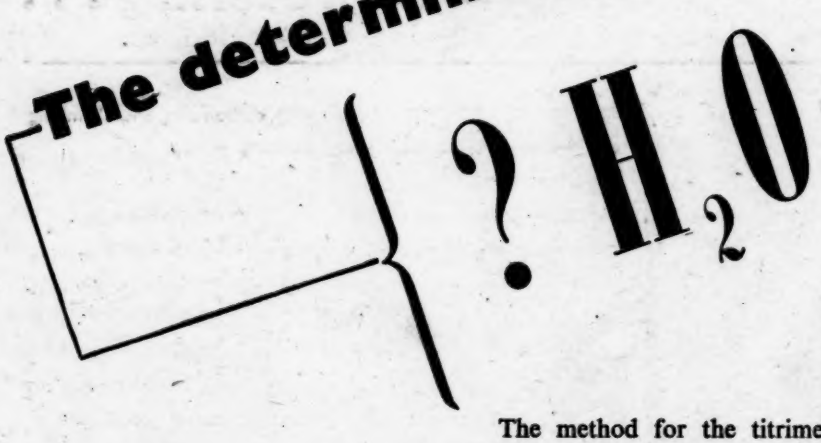
SHELL

PG2

Shell Chemicals Limited
(DISTRIBUTORS)

112, Strand, LONDON, W.C.2. *Telephone:* Temple Bar 4455

The determination of water



The method for the titrimetric determination of water suggested by Karl Fischer (*Agnew. Chem.*, 1935, **48**, 394) is widely applicable and T. G. Bonner (*Analyst*, 1946, **71**, 483) has evolved a procedure which obviates most of the difficulties previously associated with it. Karl Fischer Reagent can now be supplied in the form of two separate solutions, equal volumes of which are mixed to give the actual reagent, while the solution of water in methyl alcohol-dioxan mixture and the specially dried dioxan are also available. An illustrated pamphlet describing this modification will be supplied on request.

KARL FISCHER REAGENT	Solution No. 1 (iodine in methyl alcohol) in 500 ml. bottles, 17/6 Solution No. 2 (sulphur dioxide in pyridine) in 500 ml. bottles, 27/6
WATER SOLUTION	(approximately 5 mg. per ml.) in 1 litre bottles, 25/-
DIOXAN, DRY	in 250 ml. bottles 9/-. Containers extra

THE BRITISH DRUG HOUSES LTD.
B.D.H. LABORATORY CHEMICALS GROUP
POOLE DORSET

Telephone: Poole 962 *Telegrams: Tetradome Poole*

Rea/3

PRINTED IN GREAT BRITAIN BY RICHARD CLAY AND COMPANY, LTD., BUNGAY, SUFFOLK.

ADDITIONS TO THE LIBRARY OF THE CHEMICAL SOCIETY DURING THE YEAR 1948.

ABEGG, R., and HERZ, W. Chemisches Praktikum; experimentelle Einführung in präparative und analytische Arbeiten auf physikalisch-chemischer Grundlage. Göttingen 1900. pp. 114.

ABREU, B. E. *See* ANDERSON, H. H.

ACTA CHEMICA SCANDINAVICA. Vol. I, etc. Copenhagen. 1947 +. (*Reference.*)

ACTA CRYSTALLOGRAPHICA. *See* INTERNATIONAL UNION OF CRYSTALLOGRAPHY.

ADAMS, R. R. *See* LORIG, C. H.

AGRICULTURAL CHEMICALS. Vol. I, etc. New York 1946 +. (*Reference.*)

ALBAREDA HERRERA, J. M. El suelo: estudio fisico-químico y biológico de su formación y constitución. Madrid 1940. pp. xv + 470.

—— Origen y formación del humus. (Monografías de Ciencia Moderna, No. 4.) [Madrid] 1945. pp. 92. ill.

ALEIXANDRE, V. Compendio de química general. 3rd edition. Madrid 1947. pp. xi + 462. ill.

ALFREY, T. *See* HIGH POLYMERS. VOL. VI.

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE. Approaches to tumor chemotherapy. Edited by F. R. MOULTON. Washington 1947. pp. [x] + 442. ill.

AMERICAN PHYSICAL SOCIETY. *Division of Electron Optics.* Preparation and characteristics of solid luminescent materials. Symposium held at Cornell University, October 24—26, 1946. [Edited by G. R. FONDA and F. SEITZ.] New York 1948. pp. xv + 459. ill.

AMERICAN SOCIETY FOR TESTING MATERIALS. Symposium on pH measurement. Philadelphia 1947. pp. v + 79. ill. (*Reference.*)

AMERICAN SOCIETY OF BREWING CHEMISTS. Proceedings. Annual Meetings, 1946—47. Sawyer, Wis. 1946—47. pp. [viii] + 152, [viii] + 147. ill. (*Reference.*)

ANDERSON, C. L. *See* WASHINGTON, UNIVERSITY OF. Publications in Fisheries.

ANDERSON, H. H., MURAYAMA, F., and ABREU, B. E. Pharmacology and experimental therapeutics; a survey for 1941—46. Berkeley 1947. pp. viii + 368.

ANDRADE, E. N. DA C. The atom and its energy. London 1947. pp. [xii] + 196. ill.

—— Viscosity and plasticity; being the substance of three post-graduate lectures to the Oil and Colour Chemists' Association. Cambridge 1947. pp. 82. ill.

ANGELL. F. G. *See* BAYLEY, T.

ANNUAL REVIEW OF MICROBIOLOGY. Vol. I, etc. Stanford 1947 +. (*Reference.*)

ANSCHÜTZ, L. *See* RICHTER, VICTOR VON.

ANSCHÜTZ, R. *See* RICHTER, VICTOR VON.

ASHMORE, S. A. *See* MINISTRY OF SUPPLY. *Chemical Research and Development Establishment.*

ASSOCIATION OF BRITISH CHEMICAL MANUFACTURERS. Safety rules for use in chemical works. Part I. Model rules. 3rd edition. London 1947. pp. 69. (*Reference.*)

ASSOCIATION OF NEW YORK STATE CANNERS. *See* OHIO CANNERS' ASSOCIATION.

ASTON, F. W. The structural units of the material universe. (7th Earl Grey Memorial Lecture.) London 1925. pp. 23. ill.

AUSTIN, R. G. Aids to qualitative inorganic analysis. 2nd edition. London 1947. pp. xii + 207. ill.

AUSTRALIA, COMMONWEALTH OF. *Department of Munitions.* Munitions Supply Laboratories. Information Circular No. 8. Silica aerogels. By A. A. ROSENBLUM. Maribyrnong 1947. pp. 14.

AVERY, G. S., and JOHNSON, E. B. Hormones and horticulture. The use of special chemicals in the control of plant growth. New York 1947. pp. xi + 326. ill.

BAILEY, A. E. [Editor.] Cottonseed and cottonseed products: their chemistry and technology. New York 1948. pp. xxiii + 936. ill.

BAILEY, M. I. A study of the gelation of frozen egg magma. New York 1932. pp. 33. ill.

BALCH, R. T. *See* SUGAR RESEARCH FOUNDATION, INC. Technological Report Series, No. 3.

BARCELÓ-MATUTANO, J. R. Introducción a la espectroquímica: con indicación de otros métodos ópticos de interes en la química analítica. Barcelona 1946. pp. 156. ill.

BARRON, H. Modern rubber chemistry. 2nd edition. London 1947. pp. viii + 502. ill.

BARY, P. Les origines de la chimie colloïdale. A. Baudrimont (1806—1880). Paris [1928]. pp. 78. ill.

BASSETT, H. *See* EWENS, R. V. G.

BASU, K. P. Studies on protein, fat and mineral metabolism in Indians. (*Special Report, Indian Research Fund Association*, No. 15.) Cawnpore 1946. pp. ii + 64.

BAUER, M. Lehrbuch der Mineralogie. Berlin 1886. pp. xi + 562. ill.

BAWN, C. E. H. The chemistry of high polymers. London 1948. pp. x + 249. ill.

BAYLEY, T. A pocket book for chemists, [etc.]. 10th edition. Edited by F. G. ANGELL. London 1948. pp. xv + 508. (*Reference.*)

BECHLER, H. *See* WEBER, H.

BELL, D. J. Introduction to carbohydrate biochemistry. 2nd edition. London 1948. pp. viii + 107.

BELL, [SIR WILLIAM JAMES]. Sale of food and drugs. 12th edition. By R. A. ROBINSON. London 1947. pp. xlviii + 529 + 71.

BENDER, C. B. *See* SUGAR RESEARCH FOUNDATION, INC. Technological Report Series, No. 4.

BENGAL. *Directorate of Industries.* Bulletin No. 129. An improved method of making sugar-candy (with special reference to palm-candy or Tal-Misri). By H. BHATTACHARYYA. Alipore 1947. pp. 30. ill.

BENNETT, H. Practical emulsions. 2nd edition. Brooklyn 1947. pp. xvi + 568. *(*Reference.*)

BERGMANN, E. D. Isomerism and isomerisation of organic compounds. New York 1948. pp. xi + 138.

BERNHEIM, F. The interaction of drugs and cell catalysts. [2nd edition.] Minneapolis 1946. pp. iv + 107.

BERRY, A. J. Modern chemistry : some sketches of its historical development. Cambridge 1946. pp. x + 240.

—— Qualitative inorganic analysis. 2nd edition. Cambridge 1948. pp. viii + 155.

BETHE, H. A. Elementary nuclear theory. New York 1947. pp. vi + 147.

BHATTACHARYYA, H. *See* BENGAL. *Directorate of Industries.*

BIGELOW, W. D. *See* NATIONAL CANNERS' ASSOCIATION. *Research Laboratory.*

BIKERMAN, J. J. Surface chemistry for industrial research. New York 1948. pp. ix + 464. ill.

BINKLEY, W. W. *See* SUGAR RESEARCH FOUNDATION, INC. Scientific Report Series, No. 10.

BIOLOGICAL SYMPOSIA. Vol. XII. Edited by W. J. DANN and G. H. SATTERFIELD. Estimation of the vitamins. Lancaster, Pa. 1947. pp. [x] + 531. ill.

BLATT, A. H. *See* CONANT, J. B.

BÖCKMANN, F. Das Celluloid. 3rd edition. Wien [1906]. pp. viii + 132. ill.

BOOTH, A. D. Fourier technique in *X*-ray organic structure analysis. Cambridge 1948. pp. viii + 106. ill.

BOYD, W. C. Fundamentals of immunology. 2nd edition. New York 1947. pp. xvi + 503. ill.

BREDIG, G. Über die Chemie der extremen Temperaturen. Leipzig 1901. pp. 32.

BRITISH CHEMICAL DIGEST. Vol. I, etc. Beckenham 1946 +. (*Reference.*)

BRITISH INTERNATIONAL PLASTICS ANNUAL, 1947. London 1947. pp. 183. ill. (*Reference.*)

BRITISH LEATHER MANUFACTURERS' RESEARCH ASSOCIATION. Progress in leather science, 1920—45. Issued in commemoration of the twenty-fifth anniversary of the formation of the British Leather Manufacturers' Research Association. 3 vols. London 1946—48. pp. viii + 220; xi + 221—485; xii + 486—705. ill.

BRITISH NON-FERROUS METALS RESEARCH ASSOCIATION. *Research Reports.* R.R.A. 635. Metallography of some aluminium alloys. By M. D. SMITH. London 1943. pp. 12. ill.

BRITISH OXYGEN CO., LTD. Oxygen : its potentialities in iron and steel production. London 1948. pp. v + 52. ill.

BRITISH PHARMACOPŒIA 1948. London 1948. pp. xl + 914. (*Reference.*)

BRITISH PLASTICS YEARBOOK, 1948. London 1948. pp. 479. ill. (*Reference.*)

BRITISH RUBBER DEVELOPMENT BOARD. Rubber Developments. Vol. I, etc. 1947 +. (*Reference.*)

BROGLIE, L. DE. Licht und Materie. 6th edition. (Ergebnisse der neuen Physik.) Hamburg 1944. pp. 329.

BROWN, H. [and others]. Aluminum and its applications. New York 1948. pp. xiii + 338. ill.

BROWN, S. P. Air conditioning and elements of refrigeration. New York 1947. pp. ix + 644. ill.

BROWN, W. J. Fabric reinforced plastics. London 1947. pp. 148. ill.

BRUGES, E. A. *See* GEYER, E. W.

BRUSSET, H. Contribution a l'étude du carbone et des charbons mineraux. Paris 1948. pp. [viii] + 89. ill.

BUCHAN, S. Rubber to metal bonding. London 1948. pp. xiv + 239. ill.

BUDGEN, N. F. Aluminium and its alloys. 2nd edition. London 1947. pp. ix + 369. ill.

BULLENS, D. K., and others. Steel and its heat treatment. 5th edition. Vols. I & II. New York 1948. pp. xxxii + 489, xxiv + 293. ill.

BURFORD, W. B. *See* FOWLER, R. D.

BURK, R. E., and GRUMMITT, O. Chemical architecture. (Frontiers in Chemistry, Vol. V.) New York 1948. pp. [xiv] + 202. ill.

BUSCARONS UBEDA, F. Análisis inorgánico cualitativo sistemático. 2nd edition. Barcelona 1944. pp. 147.

BUTTREY, D. N. Cellulose plastics. London 1947. pp. 127. ill.

CALLAHAN, L. I. Russian-English technical and chemical dictionary. New York 1947. pp. xvii + 794. (*Reference.*)

CAMERON, A. T. *See* SUGAR RESEARCH FOUNDATION, INC. Scientific Report Series, No. 9.

CANADA, DOMINION OF. *Department of Agriculture.* Bulletin No. 90—N.S. Dehydration of fruits and vegetables in Canada; a summary of four years work. Ottawa 1927. pp. 29. ill.

—— *Honorary Advisory Council for Scientific and Industrial Research.* Report No. 11. The red discolouration of cured codfish. By F. C. HARRISON and M. E. KENNEDY. Ottawa 1922. pp. 18.

—— —— Report No. 12. The discolouration, smut, or blackening of canned lobster. By F. C. HARRISON and E. G. HOOD. Ottawa 1923. pp. 40. ill.

—— *National Research Council.* Report No. 19. The bacteriology of certain sea fish. By F. C. HARRISON, H. M. PERRY, and P. W. P. SMITH. Ottawa 1926. pp. 48.

CARNAUD, J. J., and FORGES DE BASSE-INDRE. *Laboratoire de Recherches.* Bulletin No. 8. Méthodes actuelles de l'industrie des conserves de tomates aux États-Unis. Paris 1948. pp. viii + 95. ill.

CARSLAW, H. S., and JAEGER, J. C. Conduction of heat in solids. Oxford 1947. pp. viii + 386. ill.

CASARES GIL, J. Tratado de análisis químico. 4th edition. Vol. II. Madrid 1935. pp. xv + 973. ill.

CASTNER-KELLNER ALKALI CO. Fifty years of progress, 1895—1945. [1947.] pp. [vi] + 65. ill.

CEMENT AND CONCRETE ASSOCIATION. *Library Information Bulletin.* Publications on cement and concrete in London libraries. London 1947. pp. 79. (*Reference.*) [In typescript.]

CEYLON. *Rubber Commission.* Report. Colombo 1947. pp. 137. ill.

CHATFIELD, H. W. Varnish constituents. 2nd edition. London 1947. pp. xx + 592. ill.

CHEMICAL CORPS ASSOCIATION. The chemical warfare service in World War II : a report of accomplishments. Washington 1948. pp. 222. ill.

CHEMICAL INSTITUTE OF CANADA. Proceedings of the Conference on Nuclear Chemistry at McMaster University, Hamilton, Canada, May 15, 16 and 17, 1947. Parts I and II. Ottawa 1947. pp. xii + 119, viii + 120—228. ill. (Two copies.)

—— The professions of chemistry and chemical engineering in Canada. By L. H. CRAGG. [Ottawa] 1948. pp. iv + 33.

CHEMICAL PROGRESS. Handbook of an Exhibition held at the Science Museum, July to September, 1947, by the CHEMICAL SOCIETY and the DEPARTMENT OF SCIENTIFIC AND INDUSTRIAL RESEARCH as part of the Centenary Celebrations of the Chemical Society. London 1947. pp. [iv] + 80. (Two copies.)

CHEMICAL SOCIETY. *See* CHEMICAL PROGRESS.

CHERONIS, N. D., and ENTRIKIN, J. B. Semimicro-qualitative organic analysis. New York 1947. pp. xiv + 498. ill.

CHOVIN, P. *See* MOUREU, C.

CHYMIA. Annual studies in the history of chemistry. Editor-in-chief : T. L. DAVIS. Vol. I. Philadelphia 1948. pp. xiv + 190. ill. (*Reference.*)

CLARK, E. D. *See* WASHINGTON, UNIVERSITY OF. Publications in Fisheries.

CLAUS, C. Fragment einer Monographie des Platin's und der Platinmetalle, 1865—83. St. Petersburg 1883. pp. v + 62. [Photostat copy.] (*Reference.*)

CLOUGH, R. W. *See* WASHINGTON, UNIVERSITY OF. Publications in Fisheries.

COHEN, J. B. Organic chemistry for advanced students. 3rd edition. 3 vols. London 1921. pp. viii + 366; viii + 435; viii + 378. ill.

COLD SPRING HARBOR. *Biological Laboratory.* Symposia on quantitative biology. Vol. XI. Heredity and variation in micro-organisms. New York 1946. pp. xii + 314. ill. (*Reference.*)

—— —— Symposia on quantitative biology. Vol. XII. Nucleic acids and nucleo-proteins. New York 1946. pp. xii + 279. ill. (*Reference.*)

COMENGE, M. Análisis de alimentos. 2nd edition. Madrid 1936. pp. xvi + 648. ill.

—— La vid y los vinos españoles. Madrid 1942. pp. [viii] + 237. ill.

CONANT, J. B., and BLATT, A. H. The chemistry of organic compounds; a year's course in organic chemistry. 3rd edition. New York 1947. pp. ix + 665. ill.

CONFERENCE ON BIOLOGICAL ANTIOXIDANTS, 1ST. Transactions. Edited by C. G. MACKENZIE. Sponsored by the JOSIAH MACY, JR. FOUNDATION. New York [1947]. pp. [vi] + 81. (*Reference.*)

COOKE, E. I. *See* GARDNER, W.

CORRIE, F. E. Some elements of plants and animals. London 1948. pp. x + 120.

COSSLETT, V. E. The electron microscope. London 1947. pp. viii + 128. ill.

COTTRELL, A. H. Theoretical structural metallurgy. London 1948. pp. viii + 256. ill.

COWARD, K. H. The biological standardisation of the vitamins. 2nd edition. London 1947. pp. vii + 224. ill.

CRAGG, L. H. *See* CHEMICAL INSTITUTE OF CANADA.

CRUESS, W. V. Commercial fruit and vegetable products. 3rd edition. New York 1948. pp. x + 906. ill.

CUMANN CEIMICIDHE NA HEIREANN. Irisleabhar. Irish Chemical Association Journal, 1946—47, etc. Dublin 1947 +.

DALE, SIR HENRY. *See* ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND.

DALLAVALLE, J. M. Micromeritics; the technology of fine particles. 2nd edition. New York 1948. pp. xxviii + 555. ill.

DANN, W. J. *See* BIOLOGICAL SYMPOSIA. Vol. XII.

DARKEN, M. F. *See* RICHTER, VICTOR VON.

DAVIS, R. H. Breathing in irrespirable atmospheres and, in some cases, under water. London [1947]. pp. xi + 386. ill.

DAVIS, T. L. *See* CHYMIA.

DAVISON, W. H. T. *See* ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND.

DEPARTMENT OF SCIENTIFIC & INDUSTRIAL RESEARCH. *Building Research Station.* Note No. A 10, etc. Watford 1947 +. (*Reference.*)

—— *National Physical Laboratory.* The inclusion of equivalent metric values in scientific papers. London 1945. pp. 15. ill. (Two copies.)

—— *Road Research Laboratory.* Road note No. 2, etc. London 1947 +. (*Reference.*)

—— *See* CHEMICAL PROGRESS.

DETHIER, V. G. Chemical insect attractants and repellents. London 1947. pp. xv + 289. ill.

DIEHL, H. Electrochemical analysis with graded cathode potential control. Columbus 1948. pp. vii + 56. ill.

DODGE, F. W. *See* HOUGEN, O. A.

DOUTHWAITE, A. H. *See* HALE-WHITE, W.

DRUCE, J. G. F. Rhenium, dvi-manganese, the element of atomic number 75. Cambridge 1948. pp. viii + 92.

DRUMMOND, SIR JACK. *See* ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND.

DUJARDIN, J. *See* RUAU, L.

DUNSHEATH, P. *See* INDUSTRIAL RESEARCH.

DUSTIN, P., JUN. *See* EIGSTI, O. J.

EASTMAN, E. D., and ROLLEFSON, G. K. Physical chemistry. New York 1947. pp. viii + 504. ill.

EASTWOOD, T. *See* ELLIS, C.

EIGSTI, O. J. Colchicine bibliography. With a supplement by P. DUSTIN, JUN. (From *Lloydia*, 1947, 10.)

EILERS, H., SAAL, R. N. J., and WAARDEN, M. VAN DER. Chemical and physical investigations on dairy products. (Monographs on the Progress of Research in Holland during the war.) Amsterdam 1947. pp. xiii + 215. ill.

EINSTEIN, A., and INFELD, L. The evolution of physics. London 1938. pp. x + 319. ill.

ELECTROCHEMICAL SOCIETY. Journal. Vol. 93, etc. Baltimore 1948 +.

—— The corrosion handbook. Edited by H. H. UHLIG. New York 1948. pp. xxxiii + 1188. ill.

ELECTRODEPOSITORS' TECHNICAL SOCIETY. Proceedings of the 3rd International Conference on electrodeposition, 1947. London 1948. pp. [ii] + 219. ill.

ELLIS, C., and SWANEY, M. W. Soilless growth of plants. 2nd edition. Revised and enlarged by T. EASTWOOD. New York 1947. pp. x + 277. ill.

ELLIS, L. *See* MINISTRY OF SUPPLY. *Chemical Research and Development Establishment.*

ELSEVIER'S ENCYCLOPÆDIA OF ORGANIC CHEMISTRY. Edited by E. JOSEPHY and F. RADT. Series III. Carboisocyclic condensed compounds. Vols. 12A, 13, 14. New York 1948, 1946, 1940. pp. xxviii + 1262; xx + 1265; xx + 711. (*Reference.*)

ENTRIKIN, J. B. *See* CHERONIS, N. D.

EPHRAIM, F. Inorganic chemistry. 5th edition. By P. C. L. THORNE and E. R. ROBERTS. London 1948. pp. xii + 939. ill.

EVANS, T. H. *See* SUGAR RESEARCH FOUNDATION, INC. Scientific Report Series, No. 6.

EVANS, U. R. An introduction to metallic corrosion. London 1948. pp. xxxvi + 211. ill.

EWENS, R. V. G., and BASSETT, H. Inorganic chemical nomenclature. 1948. pp. 19. [Unpublished typescript.]

FAHRION, W. Die Fabrikation der Margarine, des Glyzerins und Stearins. Berlin 1920. pp. 135.

FARADAY, M. *See* MARTIN, T.

FARADAY SOCIETY. Discussions. No. 1, etc. London 1947 +.

FEIGL, F. Qualitative analysis by spot tests: inorganic and organic applications. 3rd English edition, translated by R. E. OESPER. New York [1946]. pp. xvi + 574. ill.

FELLERS, C. R. *See* WASHINGTON, UNIVERSITY OF. Publications in Fisheries.

FERGUSON, A. *See* PHILOSOPHICAL MAGAZINE.

FERNANDEZ-LADREDA, J. M. *See* MARTINEZ VIVAS, J.

FIAT REVIEW OF GERMAN SCIENCE, 1939—1946. Bacteriology and immunology. By H. SCHMIDT. Wiesbaden 1947. pp. [xii] + 155. (Two copies.)

—— General metallurgy. By M. HANSEN [and others]. Wiesbaden 1948. pp. [viii] + 295. (Two copies.)

—— Non-ferrous metallurgy. Parts I and II. By M. HANSEN [and others]. Wiesbaden 1948. pp. [viii] + 207; pp. [iv] + 171. (Two copies.)

—— Physics of solids. Part I. By G. JOOS [and others]. Wiesbaden 1947. pp. [xvi] + 228. ill. (Two copies.)

FIELD, J. W. *See* MALAYAN UNION. *Malaria Advisory Board.*

FINDLAY, A. Chemistry in the service of man. 7th edition. London 1947. pp. xx + 390. ill.

FISCHER, E. Exercises in the preparation of organic compounds. Translated from the 4th German edition by A. KLING. Glasgow 1896. pp. viii + 80. ill.

FITZGERALD, F. F. *See* NATIONAL CANNERS' ASSOCIATION. *Research Laboratory.*

FLAGG, J. F. Organic reagents used in gravimetric and volumetric analysis. (Chemical Analysis, Vol. 4.) New York 1948.

FOLLETT, D. H. The electron jubilee exhibition. London 1947. pp. 48. ill.

FONDA, G. R. *See* AMERICAN PHYSICAL SOCIETY. *Division of Electron Optics.*

FOOD TECHNOLOGY. Vol. I, etc. Champaign 1947 +. (*Reference.*)

FORGES DE BASSE-INDRE. *See* CARNAUD, J. J.

FOWLER, R. D., and BURFORD, W. B. Fluorocarbons. Washington [1947]. pp. [xii] + 147. ill. (*Reference.*)

FREEMAN, J. A. *See* MINISTRY OF FOOD.

FULTON, J. F., and THOMSON, E. H. Benjamin Silliman, 1779—1864. Pathfinder in American science. New York 1947. pp. ix + 294. ill.

FURNAS, C. C. *See* INDUSTRIAL RESEARCH INSTITUTE, INC.

FUSON, R. C. *See* SHRINER, R. L.

GALE, E. F. The chemical activities of bacteria. London 1947. pp. [v] + 199. ill.

GALVÃO, P. E. Sobre a aplicação intraespecifica da lei da superficie nas regiões tropicais. São Paulo 1942. pp. 41.

GALVEZ MORALES, N. Curso de química para biólogos. Madrid 1946. pp. 670. ill.

GAMBLE, J. L. Chemical anatomy, physiology and pathology of extracellular fluid. A lecture syllabus. 5th edition. Cambridge, Mass. 1947. pp. [160]. ill. (*Reference.*)

GARDNER, W. Chemical synonyms and trade names. A dictionary and commercial handbook. 5th edition, revised and enlarged by E. I. COOKE. Kingston Hill 1948. pp. [viii] + 558. (*Reference.*)

GARNER, C. S. *See* YOST, D. M.

GARNER, W. W. The production of tobacco. Philadelphia 1946. pp. xiii + 516. ill.

GAUGER, A. W. Physical chemistry and the technology of fuels. (21st Annual Priestley Lectures.) Pennsylvania 1947. pp. vii + 114. ill.

GAYDON, A. G. Dissociation energies and spectra of diatomic molecules. London 1947. pp. xi + 239. ill.

—— Spectroscopy and combustion theory. 2nd edition. London 1948. pp. xii + 242. ill.

GEDDES, A. ST.-CLAIR. The advertising of chemicals and allied products. London 1947. pp. xi + 232. ill.

GENEVOIS, L., and RIBEREAU-GAYON, J. Le vin. Paris 1947. pp. 150.

GEYER, E. W., and BRUGES, E. A. Tables of properties of gases, with dissociation theory and its applications. London 1948. pp. 102. ill. (*Reference.*)

GIRAL, F. Productos químicos y farmaceuticos. A base de la obra " Preparación de productos químicos y químico-farmaceuticos " por C. A. ROJAHN. 3 vols. Mexico, D.F. 1946. pp. xxxvii + 693, 694—1510, 1511—2226.

GLASGOW, UNIVERSITY OF. *Chemistry Department.* Separation and identification of organic compounds. London 1948. pp. 20.

GOEPP, R. M., JUN. *See* PIGMAN, W. W.

GÖTTINGEN, AKADEMIE DER WISSENSCHAFTEN. Nachrichten. Biologisch-physiologisch-chemische Abteilung. Year 1946 etc. Göttingen 1946 +. (*Reference.*)

—— —— Mathematisch-physikalisch-chemische Abteilung. Year 1946 etc. Göttingen 1946 +. (*Reference.*)

GOODALL, D. W. *See* IMPERIAL BUREAU OF HORTICULTURE AND PLANTATION CROPS.

GORDON, M. *See* ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND.

GORTER, C. J. Paramagnetic relaxation. Amsterdam 1947. pp. vii + 127. ill.

GOVERNMENT CHEMIST, DEPARTMENT OF. *See* MINISTRY OF SUPPLY. *Chemical Research and Development Establishment.*

GRAHAM, G. *See* HUTCHISON, R.

GRANT, J. Wood pulp and allied products. 2nd edition. London 1947. pp. xvi + 312. ill.

GREGORY, F. G. *See* IMPERIAL BUREAU OF HORTICULTURE AND PLANTATION CROPS.

GROOT, S. R. DE. L'effet Soret. Diffusion thermique dans les phases condensées. Amsterdam 1945. pp. viii + 191. ill.

GRUMMITT, O. *See* BURK, R. E.

GUENTHER, E. The essential oils. Vol. I. History—origin in plants—production—analysis. New York 1948. pp. xvi + 427. ill.

HAIM, G., and ZADE, H. P. Welding of plastics. London 1947. pp. xv + 206. ill.

HALDANE, J. B. S. Callinicus: a defence of chemical warfare. London 1925. pp. viii + 84.

HALE-WHITE, W. Materia medica, pharmacy, pharmacology and therapeutics. 27th edition. Revised by A. H. DOUTHWAITE. London 1947. pp. x + 49. (*Reference.*)

HALL, J. D. Industrial applications of infra-red. New York 1947. pp. x + 201. ill.

HAMILTON, L. F., and SIMPSON, S. G. Calculations of analytical chemistry. 4th edition. New York 1947. pp. xiii + 387. ill.

HAND- UND JAHRBUCH DER CHEMISCHEN PHYSIK. Vol. II. Part 3C. Chemische Morphologie der Flüssigkeiten und Kristalle. By C. WEYGAND. [Leipzig 1941]. pp. 192. ill.

HANSEN, A. *See* JØRGENSEN, A.

HANSEN, M. *See* FIAT REVIEW OF GERMAN SCIENCE, 1939—46.

HARKINS, L. B. Magnesium fabrication. New York 1947. pp. vii + 149. ill.

HARRINGTON, R. H. The modern metallurgy of alloys. New York 1948. pp. xii + 209. ill.

HARRISON, F. C. *See* CANADA, DOMINION OF. *Honorary Advisory Council for Scientific and Industrial Research.*

—— *See* CANADA, DOMINION OF. *National Research Council.*

HARRY, R. G. Principles and practice of modern cosmetics. Vol. 2. Cosmetic materials; their origin, characteristics, uses and dermatological action. London 1948. pp. xi + 479. ill. (*Reference.*)

HASWELL, C. H. Stabilization of soils by the use of bitumen emulsion. Simla 1935. pp. viii + 14. ill.

HATCHER, W. H. An introduction to chemical science. New York 1940. pp. viii + 423. ill.

HAUGHTON, J. L. Bibliography of the literature relating to constitutional diagrams of alloys. (Institute of Metals Monograph and Report Series, No. 2.) London 1942. pp. [iv] + 163. (*Reference.*)

HAUSNER, H. H. Powder metallurgy: principles and methods. Brooklyn, N.Y. 1947. pp. vii + 307. ill.

HENRICH, F. Theorien der organischen Chemie. 5th edition. Braunschweig 1924. pp. viii + 515.

HERZ, W. *See* ABEGG, R.

HEVESY, G. Radioactive indicators: their application in biochemistry, animal physiology, and pathology. New York 1948. pp. xviii + 556. ill.

HEWITT, L. F. *See* LONDON COUNTY COUNCIL.

HIBBERT, H. *See* SUGAR RESEARCH FOUNDATION, INC. Scientific Report Series, No. 6.

HICKINBOTTOM, W. J. Reactions of organic compounds. 2nd edition. London 1948. pp. x + 481. ill.

HIGH POLYMERS. Vol. VI. Mechanical behaviour of high polymers. By T. ALFREY. New York 1948. pp. xiv + 581. ill.

HIMUS, G. W. The elements of fuel technology. London 1947. pp. xvi + 506. ill.

HOFFMANN, B. The strange story of the quantum. New York 1947. pp. xi + 239. ill.

HOOD, E. G. *See* CANADA, DOMINION OF. *Honorary Advisory Council for Scientific and Industrial Research.*

HOPKINS, E. S. Water purification control. 3rd edition. Baltimore 1948. pp. x + 289. ill.

HOUGEN, O. A., and DODGE, F. W. The drying of gases. Ann Arbor 1947. pp. ix + 199. ill.

HOWE, J. L. [and others]. Bibliography of the platinum metals, 1918—1930. Newark, N.J. 1947. pp. 138. (*Reference.*)

HOYOS DE CASTRO, A. Geoquímica. I. Parte general. II. Parte especial. (Monografías de Ciencia Moderna, No. 2.) [Madrid] 1945. pp. 98, 104. ill.

HUME-ROTHERY, W. Atomic theory for students of metallurgy. (Institute of Metals Monograph and Report Series, No. 3.) London 1946. pp. viii + 286. ill.

HUSTON, R. C. A correlation of some physical properties of alkanes and alkenes. Boiling points, molecular volumes and surface tensions. East Lansing 1947. pp. 96. ill.

HUTCHISON, G. L. *See* MINISTRY OF SUPPLY. *Chemical Research and Development Establishment.*

HUTCHISON, R. Food and the principles of dietetics. 10th edition. Revised by V. H. MOTTRAM and G. GRAHAM. London 1948. pp. xxviii + 727. ill.

ILLINOIS INSTITUTE OF TECHNOLOGY. Research Publications. Corrosion. Chicago 1948. pp. [ii] + [59]. ill.

—— —— Molecular spectra II. Chicago 1948. pp. 62. ill.

IMPERIAL BUREAU OF HORTICULTURE AND PLANTATION CROPS. Technical Communication No. 17. Chemical composition of plants as an index of their nutritional status. By D. W. GOODALL and F. G.

GREGORY. East Malling 1947. pp. 167. (*Reference.*)

IMPERIAL COLLEGE CHEMICAL ENGINEERING SOCIETY. Journal. Vol. 1, etc. London 1945 + (*Reference.*)

INDIA RUBBER WORLD. Compounding ingredients for rubber. 2nd edition. New York 1947. pp. 640. (*Reference.*)

INDUSTRIAL FINISHING. Vol. 1, etc. Leighton Buzzard 1948 +.

INDUSTRIAL RESEARCH. Advisory Editor: P. DUNSHEATH. London 1947. pp. 535. (*Reference.*)

INDUSTRIAL RESEARCH INSTITUTE, INC. Research in industry: its organization and management. Edited by C. C. FURNAS. New York 1948. pp. xii + 574. ill.

INDUSTRIES DES PLASTIQUES. Vol. 2, etc. Paris 1946 + (*Reference.*)

INFELD, L. *See* EINSTEIN, A.

INFIESTA MOLERO, J. L. DE LA. Aspectos químicos de la moderna tecnica de carburantes. (Monografías de Ciencia Moderna, No. 3.) [Madrid] 1945. pp. 84. ill.

INSTITUT INTERNATIONAL DE CHIMIE SOLVAY. Septième Conseil de Chimie, 1947. Rapports et discussions sur les isotopes. Bruxelles 1948. pp. 411. ill. (*Reference.*)

INSTITUTE OF PETROLEUM. Standard methods for testing petroleum and its products. 9th edition. London 1948. pp. xlviii + 616. ill.

INSTITUTION OF MINING ENGINEERS. Transactions. Vol. 104, No. 6, etc. London 1946 +. (*Reference.*)

INTERNATIONAL UNION OF CRYSTALLOGRAPHY. Acta Crystallographica. Vol. I, etc. Cambridge 1948 +. (*Reference.*)

IPIÉNS LACASA, A. Elementos de química. 5th edition. Vol. I. Química inorgánica. Vol. II. Química orgánica. Madrid 1944. pp. xi + 426; xii + 397. ill.

IRISH CHEMICAL ASSOCIATION and ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND. Proceedings of a colloquium on the industrial utilisation of agricultural products and of seaweed. Dublin 1947. pp. 71. ill.

IRISH CHEMICAL ASSOCIATION JOURNAL. *See* CUMANN CEIMICIDHE NA hEIREANN.

JACKSON, P. G. Boiler feed water. A concise handbook of water for boiler feeding purposes. 4th edition. London 1947. pp. xii + 132. ill.

JAEGER, J. C. *See* CARSLAW, H. S.

JARVIS, N. D. *See* WASHINGTON, UNIVERSITY OF. Publications in Fisheries.

JENKINS, I. Controlled atmospheres for the heat treatment of metals. London 1946. pp. x + 532. ill.

JENNISON, F. H. The manufacture of lake pigments from artificial colours. London 1900. pp. vii + 136. ill.

JNANANANDA, S. High vacua; principles, production and measurement. New York 1947. pp. xiii + 310. ill.

JØRGENSEN, A. Micro-organisms and fermentation. 15th edition. By A. HANSEN. London 1948. pp. 589. ill.

JOHNSON, A. W. *See* ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND.

JOHNSON, E. B. *See* AVERY, G. S.

JOOS, G. *See* FIAT REVIEW OF GERMAN SCIENCE, 1939—46.

JORDAN, S., and LANGWILL, K. E. Confectionery analysis and composition. Chicago 1946. pp. viii + 116.

JOSEPHY, E. *See* ELSEVIER'S ENCYCLOPÆDIA OF ORGANIC CHEMISTRY.

JOSIAH MACY, JR. FOUNDATION. *See* CONFERENCE ON BIOLOGICAL ANTIOXIDANTS.

JOURNAL OF BACTERIOLOGY. *See* SOCIETY OF AMERICAN BACTERIOLOGISTS.

KAPP, R. O. The presentation of technical information; based on four public lectures given at University College, London. London 1948. pp. xii + 147.

KARRER, P. Organic chemistry. 3rd English edition. Amsterdam 1947. pp. xx + 957. ill.

KENDALL, C. E. *See* ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND.

KENNEDY, M. E. *See* CANADA, DOMINION OF. *Honorary Advisory Council for Scientific and Industrial Research.*

KIRK, R. E., and OTHMER, D. F. Encyclopedia of chemical technology. Vol. I, etc. New York 1947 +. ill. (*Reference.*)

KIRKBRIDE, C. G. Chemical engineering fundamentals. New York 1947. pp. xi + 419. ill.

KLING, A. *See* FISCHER, E.

KOBE, K. A. Inorganic process industries. New York 1948. pp. viii + 371. ill.

KOCHESHKOV, K. A. *See* UNION OF SOCIALIST SOVIET REPUBLICS. *Institute of Organic Chemistry.*

KRASNOSSELSKAJA, T. A. *See* TSWETT, M. S.

KRUMBHAAR, W. Coating and ink resins: a technological study. New York 1947. pp. v + 318. ill.

KUNSTSTOFFE. Vol. 37, etc. Münich 1947 +. (*Reference.*)

LAFARGE ALUMINOUS CEMENT CO., LTD. The characteristics of Ciment Fondu. 6th edition. London [1947]. pp. 60. ill.

—— Refractory concrete. London [1947]. pp. 55.

LANE, J. C. *See* WEIL, B. H.

LANG, V. Die Fabrikation der Kunstbutter (Margarine) Kunstspeisefette und Pflanzenbutter. 5th edition. Wien 1923. pp. viii + 160. ill.

LANGWILL, K. E. *See* JORDAN, S.

LA QUE, F. L. Cast iron in the chemical and process industries. Washington 1945. pp. [iv] + 27.

LE FÈVRE, R. J. W. Dipole moments; their measurement and application in chemistry. 2nd edition. London 1948. pp. vi + 117. ill.

LESCUYER, J. Appareillage et usinage des matières plastiques. Paris 1947. pp. xii + 435. ill.

LEVI, G. R. Chimica per i Medici. 2nd edition. Milan 1948. pp. xi + 511. ill.

LEVY, H., and PREIDEL, E. E. Elementary statistics. London 1944. pp. vii + 184.

LEXOW, S. G. *See* UNIVERSIDAD NACIONAL DE CUYO. *Instituto del Petroleo.*

LINSTEAD, R. P. *See* ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND.

LINTON, R. G., and WILLIAMSON, G. Animal nutrition and veterinary dietetics. 2nd edition. Edinburgh 1943. pp. viii + 510. ill.

LITTLE, R. W. [Editor.] Flameproofing textile fabrics. (American Chemical Society Monograph Series.) New York 1947. pp. xix + 410. ill.

LOCK, A. C. Aerosols in theory and practice. 2nd edition. London 1947. pp. 59.

LONDON COUNTY COUNCIL. Oxidation–reduction potentials in bacteriology and biochemistry. 5th edition. By L. F. HEWITT. London 1948. pp. 130. ill.

LORA TAMAYO, M. Química para médicos. 4th edition. Madrid [1944]. pp. xv + 400. ill.

LORIG, C. H., and ADAMS, R. R. Copper as an alloying element in steel and cast iron. New York 1948. pp. xii + 213. ill.

LOVELL, B. Electronics. London 1947. pp. xvi + 660. ill.

LYLE, O. *See* MINISTRY OF FUEL AND POWER. *Fuel Efficiency Committee.*

LYMAN, R. A. [Editor]. American pharmacy. Vol. II. Advanced pharmacy, medical, surgical, and dental supplies, animal health pharmacy. Philadelphia 1947. pp. x + 379. ill.

MACBETH, C. Rubber in textile factories. London [1948]. pp. 135. ill.

MCFARLANE, R. A. The processing and finishing of rayon fabrics. London 1948. pp. 104. ill.

MCILROY, R. J. The chemistry of the polysaccharides. London 1948. pp. vii + 118. ill.

MACKENZIE, C. G. *See* CONFERENCE ON BIOLOGICAL ANTIOXIDANTS.

MACMUNN, C. A. Outlines of the clinical chemistry of urine. London 1889. pp. xvi + 254. ill.

MCNAB, W. Journal of experiments. [*c.* 1891—92.] pp. 128. [MS.] (*Reference.*)

MACQUER, P. J. Elements of the theory and practice of chymistry. [Translated by A. REID.] 3rd edition. Vol. I. London 1775. pp. xix + 419. ill. (*Reference.*)

MAKROMOLEKULARE CHEMIE, DIE. Vol. 1, etc. Freiburg im Breisgau 1947 +. (*Reference.*)

MALAYAN UNION. *Malaria Advisory Board.* Medical [Circular] No. 3 of 1947. Paludrine: a general review. By J. W. FIELD. Kuala Lumpur 1947. pp. v + 42. ill.

MANESCHI, E. P. P. *See* UNIVERSIDAD NACIONAL DE CUYO. *Instituto del Petroleo.*

MANN, E. A. *See* WESTERN AUSTRALIA. *Department of Agriculture.*

MANTELL, C. L. The water-soluble gums. New York 1947. pp. v + 279. ill.

MARK, H., and PROSKAUER, E. S. The science of plastics. A comprehensive source book based on the original literature for 1942—46. Vol. I. New York 1948. pp. [viii] + 632. ill. (*Reference.*)

MARSH, A. Smoke. The problem of coal and the atmosphere. London 1947. pp. 306. ill.

MARTH, P. C. *See* MITCHELL, J. W.

MARTIN, T. Faraday. London 1934. pp. 144.

MARTINEZ VIVAS, J., ROJAS FEIGENSPAN, J., and FERNANDEZ-LADREDA, J. M. Pólvoras y explosivos modernos. 2nd edition. Vol. III. Oviedo 1943. pp. 328. ill. 3rd edition. Vol. IV. Madrid 1944. pp. 416. ill. 4th edition. Vols. I, II, V. Madrid 1945—46—47. pp. 207, 426, 169. ill.

MATAGRIN, A. Manuel du savonnier. 2nd edition. Paris 1946. pp. xxii + 409. ill.

MAYONNAISE PRODUCTS MANUFACTURERS' ASSOCIATION OF AMERICA. Proceedings of the 3rd Annual Convention. Boston 1928. pp. 72. ill.

MAZUYER, G. *See* NAVES, Y. R.

MEDICAL RESEARCH COUNCIL. Medical research in war. Report of the Medical Research Council for the years 1939—45. London 1947. pp. 455. (*Reference.*)

—— Memorandum No. 18. Thyroid enlargement and other changes related to the mineral content of drinking water (with a note on goitre prophylaxis). By M. M. MURRAY, J. A. RYLE, B. W. SIMPSON, and D. C. WILSON. London 1948. pp. 39.

MEE, A. J. *See* RICHTER, VICTOR VON.

MELVILLE, H. W. The chemistry of high polymers, *and* RIDEAL, E. K. Surface chemistry. Cambridge 1948. pp. 76. ill.

MEYER, H. Anleitung zur quantitativen Bestimmung der organischen Atomgruppen. Berlin 1897. pp. viii + 115. ill.

—— —— 2nd edition. Berlin 1904. pp. xi + 202. ill.

MIGRDICHIAN, V. The chemistry of organic cyanogen compounds. (American Chemical Society Monograph Series.) New York 1947. pp. ix + 460.

MILCHWISSENSCHAFT, DIE. Vol. 2, No. 4, etc. Nürnberg 1947 +. (*Reference.*)

MINISTRY OF FOOD. Insect pests of food; the control of insects in flour mills. By J. A. FREEMAN and E. E. TURTLE. London 1947. pp. iv. + 84. ill.

MINISTRY OF FUEL AND POWER. *Fuel Efficiency Committee.* The efficient use of steam. By O. LYLE. London 1947. pp. [iv] + 912. ill.

MINISTRY OF SUPPLY. *Chemical Research and Development Establishment* and DEPARTMENT OF THE GOVERNMENT CHEMIST. Report No. 2/R/48. The surveillance of cinematograph record film during storage. By G. L. HUTCHISON, L. ELLIS, and S. A. ASHMORE. Waltham Abbey 1948. pp. [iv] + 12. ill.

MITCHELL, A. D. British chemical nomenclature. London 1948. pp. viii + 156. (*Reference.*)

MITCHELL, J. W., and MARTH, P. C. Growth regulators for garden, field, and orchard. Chicago 1947. pp. viii + 129. ill.

MOELWYN-HUGHES, E. A. The kinetics of reactions in solution. 2nd edition. Oxford 1947. pp. [viii] + 424. ill.

MOND NICKEL CO. Nickel alloy steels; a summary of their properties and applications. London [1948]. pp. 16. ill.

MONTEQUI DÍAZ DE PLAZA, D. R. Química inorgánica aplicada. 5th edition. Madrid 1945. pp. [vi] + 530. ill.

—— Análisis inorgánico cualitativo (teoría y practica). Madrid 1945. pp. iv + 356. ill.

MONTHÉARD, P. Phénoplastes, bakélites. (Matériaux de Synthèse.) Paris 1947. pp. x + 171. ill.

MORRIS, T. N. The dehydration of food, with special reference to wartime developments in the United Kingdom. London 1947. pp. vii + 174. ill.

MOTTRAM, V. H. *See* HUTCHISON, R.

MOULTON, F. R. *See* AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE.

MOUREU, C., and CHOVIN, P. Notions fondamentales de chimie organique. 11th edition. Paris 1946. pp. xxx + 828.

MÜNZEL, K. E. Über pharmazeutische Emulsionen; (insbesondere Oel-in-Wasser-Emulsionen für innerlichen Gebrauch). Zurich 1941. pp. viii + 179. ill.

MURAYAMA, F. *See* ANDERSON, H. H.

MURRAY, M. M. *See* MEDICAL RESEARCH COUNCIL. Memorandum No. 18.

MUSPRATT, J. S. Chemistry, theoretical, practical, and analytical, as applied and relating to the arts and manufactures. 2 vols. Glasgow [1860]. pp. 836, 1186. ill. (*Reference.*)

NATIONAL CANNERS' ASSOCIATION. Bulletin 96A. Canned fruits. Washington 1926. pp. 17. ill.

—— Bulletin 97A. Canned tomatoes and tomato products: method of preparation, nutritive value and recipes for use. Washington 1927. pp. 14. ill.

—— Canned peas; their preparation, nutritive value and uses. Washington 1927. pp. 14. ill.

—— The story of the canning industry. [Washington n.d.] pp. 16.

—— The story of the tin can. Washington [n.d.] pp. 11. ill.

—— *Research Laboratory*. Bulletin No. 15L. Suggestions for canning pork and beans. By W. D. BIGELOW and F. F. FITZGERALD. Washington 1927. pp. 34.

—— —— Bulletin No. 20L. The effect of hard water in canning vegetables. By W. D. BIGELOW and A. E. STEVENSON. Washington 1923. pp. 39.

—— —— Bulletin No. 21L. Tomato products; pulp, ketchup and chili sauce. By W. D. BIGELOW and A. E. STEVENSON. pp. 74. ill.

NAVES, Y. R., and MAZUYER, G. Natural perfume materials: a study of concretes, resinoids, floral oils and pomades. Translated by E. SAGARIN. New York 1947. pp. xvii + 338. ill.

NEDERLANDSCH-INDISCH INSTITUUT VOOR RUBBERONDERZOEK. Mededeelingen. No. 67, etc. Buitenzorg 1946 +. (*Reference.*)

NESMEYANOV, A. N. *See* UNION OF SOCIALIST SOVIET REPUBLICS. *Institute of Organic Chemistry.*

NETHERLANDS CHEMICAL SOCIETY. Chemistry in wartime in the Netherlands; A review of the scientific work done by Dutch chemists in the years 1940—45. Amsterdam 1947. pp. [vi] + [542].

NEW YORK STATE. *Department of Health.* Division of Sanitation. The treatment of canning wastes. Albany 1930. pp. 101. ill.

—— —— Standard methods of the Division of Laboratories and Research. 3rd edition. Baltimore 1947. pp. xxvi + 990. ill.

NEWER METHODS OF PREPARATIVE ORGANIC CHEMISTRY. Translated and revised from the German. New York 1948. pp. xiii + 657.

NICHOLLS, J. R. *See* ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND.

NIMMO, R. R. Atomic energy. (Frontiers of Science.) London 1947. pp. 201. ill.

NOELTING, E. *See* REVERDIN, F.

NORTHEASTERN WOOD UTILIZATION COUNCIL. Bulletin No. 18. Special treatments of wood. New Haven 1947. pp. 103. ill.

NORTHEY, E. H. The sulphonamides and allied compounds. (American Chemical Society Monograph Series.) New York 1948. pp. xxvii + 660.

NUCLEONICS. An international journal for techniques and applications of nuclear science. Vol. 2, etc. New York 1948 +. (*Reference.*)

ODDO, G. Trattato di chimica organica. 2nd edition. Palermo 1948. pp. xx + 1018. ill.

OESPER, R. E. *See* FEIGL, F.

OHIO CANNERS' ASSOCIATION and ASSOCIATION OF NEW YORK STATE CANNERS. Progress report on cannery waste treatment studies. Columbus [1927]. pp. 85. ill.

OIL AND COLOUR CHEMISTS' ASSOCIATION. Paint performance, its assessment by maker and user. Cambridge 1948. pp. vi + [200].

OIL & COLOUR TRADES JOURNAL. Vol. 112, etc. London 1947 +. (*Reference.*)

O'KANE, W. C. [and others]. Studies of contact insecticides. 3 parts. (New Hampshire Agricultural Experiment Station.) Durham, N.H. 1930—31. pp. 44; 15; 8. ill.

OLLARD, E. A., and SMITH, E. B. Handbook of industrial electroplating. London 1947. pp. 287. ill.

OTHMER, D. F. *See* KIRK, R. E.

OVERBEEK, J. TH. G. *See* VERWEY, E. J. W.

OXFORD UNIVERSITY JUNIOR SCIENTIFIC CLUB. The Robert Boyle Lectures. Vol. I. Oxford 1897. pp. xi + [183]. ill.

OXLEY, T. A. The scientific principles of grain storage. Liverpool 1948. pp. [vi] + 103.

PAI CHEN, T. *See* WASHINGTON, UNIVERSITY OF. Publications in Fisheries.

PALIVA A VODA, Vol. 26, No. 6/7, etc. Praha 1946 +. (*Reference.*)

PAREDES, C. A. Experiencias de extracción de penicilina. Consideraciones sobre su poder antibiótico. Quito 1947. pp. 54.

PAULING, L. General chemistry: an introduction to descriptive chemistry and modern chemical theory. San Francisco 1947. pp. vii + 595. ill.

PERRY, H. M. *See* CANADA, DOMINION OF. *National Research Council.*

PERRY, J. W. Chemical Russian, self-taught. (Contributions to Chemical Education, No. 4.) Easton 1948. pp. vii + 221.

PHILOSOPHICAL MAGAZINE. Natural philosophy through the 18th century and allied topics. Edited by A. FERGUSON. Commemoration number to mark the 150th anniversary of the foundation of the magazine. London 1948. pp. ix + 164. ill.

PIDFORD, J. H. *See* RUBBER RESEARCH INSTITUTE OF MALAYA.

PIGMAN, W. W., and GOEPP, R. M., JUN. Chemistry of the carbohydrates. New York 1948. pp. xvii + 748. ill.

PINCASS, H. Die industrielle Herstellung von Wasserstoff. Dresden 1933. pp. [viii] + 82. ill.

PINNER, A. [Editor]. Repetitorium der organischen chemie, mit besonderer Rücksicht auf die studirenden der Medicin und Pharmacie. 8th edition. Berlin 1888. pp. xvi + 596. ill.

PÖSCHL, V. Einführung in die Kolloidchemie. 6th edition. Dresden 1923. pp. xii + 158. ill.

PORTILLO MOYA, R. Introducción a la teoría y practica de la polarografía. (Monografías de la Ciencia Moderna, No. 5.) [Madrid] 1945. pp. 126. ill.

PRATT, L. S. The chemistry and physics of organic pigments. New York 1947. pp. vii + 359. ill.

PREIDEL, E. E. *See* LEVY, H.

PROSKAUER, E. S. *See* MARK, H.

RADT, F. *See* ELSEVIER'S ENCYCLOPÆDIA OF ORGANIC CHEMISTRY.

RAMSAY, SIR WILLIAM. Elements and electrons. London 1912. pp. ix + 173. ill.

READ, J. The alchemist in life, literature and art. London 1947. pp. xii + 100. ill.

—— Humour and humanism in chemistry. London 1947. pp. xxiii + 388. ill.

—— A direct entry to organic chemistry. London 1948. pp. xiii + 268. ill.

REID, A. *See* MACQUER, P. J.

REINDEL, F. *See* RICHTER, VICTOR VON.

REVERDIN, F., and NOELTING, E. Sur la constitution de la naphthaline et de ses dérivés. Mulhouse 1888. pp. 76.

REVISTA ESPAÑOLA DE FISIOLOGIA. Vol. I, etc. Barcelona 1945 +. (*Reference.*)

RIBEREAU-GAYON, J. *See* GENEVOIS, L.

RICHTER, A. A. *See* TSWETT, M. S.

RICHTER, VICTOR VON. The chemistry of the carbon compounds. Edited by RICHARD ANSCHÜTZ. 3rd English edition. Vol. IV. The heterocyclic compounds and organic free radicals. By F. REINDEL and L. ANSCHÜTZ. Translated from the 12th German edition by M. F. DARKEN and A. J. MEE. New York 1947. pp. xv + 498. (*Reference.*)

RIDEAL, E. K. *See* MELVILLE, H. W.

RIQUELME SÁNCHEZ, D. M. Blanqueo de fibras textiles. 2nd edition. (Química aplicada a la industria textil, Vol. II.) Barcelona 1947. pp. xi + 503. ill.

RIUS MIRÓ, A. Introducción a la ingeniería química. Madrid 1944. pp. xvi + 510. ill.

ROBERTS, E. R. *See* EPHRAIM, F.

ROBINSON, R. A. *See* BELL, [SIR WILLIAM JAMES].

RØRDAM, H. N. K. Studies on activity. København 1925. pp. [viii] + 103.

ROJAHN, C. A. *See* GIRAL, F.

ROJAS FEIGENSPAN, J. *See* MARTINEZ VIVAS, J.

ROLLEFSON, G. K. *See* EASTMAN, E. D.

ROSENBLUM, A. A. *See* AUSTRALIA, COMMONWEALTH OF. *Department of Munitions.*

ROTLLANT DE FRANCH, M. *See* SANTOS RUIZ, A.

ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND. The Chemical Research Laboratory, Teddington. By R. P. LINSTEAD. London 1948. pp. 12.

ROYAL INSTITUTE OF CHEMISTRY OF GREAT BRITAIN AND IRELAND. Chemical ciphering. A universal code as an aid to chemical systematics. By M. GORDON, C. E. KENDALL, and W. H. T. DAVISON. London 1948. pp. 46.

—— The determination of alcohol. By J. R. NICHOLLS. (3rd Tatlock Memorial Lecture.) London 1948. pp. 26. ill.

—— The Fertilisers and Feeding Stuffs Act and some analytical implications. (30th Streatfeild Memorial Lecture.) London 1948. pp. 23.

—— Lecture on chemistry and medicinal treatment. By SIR HENRY DALE. (3rd Dalton Lecture.) London 1948. pp. 15.

—— Lecture on some applications of acetylenic compounds in organic synthesis. (Meldola Medal Lecture.) By A. W. JOHNSON. London 1948. pp. 18.

—— Nutritional requirements of man in the light of wartime experience. By SIR JACK DRUMMOND. (11th Gluckstein Memorial Lecture.) London 1948. pp. 23.

—— *Committee on the Education and Training of Laboratory Technicians.* Interim Report. London 1947. pp. 24.

—— *See* IRISH CHEMICAL ASSOCIATION.

RUAU, L., and SALLERON, J. Tables de conversion des richesses en alcool pur déterminées par l'alcoomètre de Gay-Lussac & par l'alcoomètre légal 1884 en richesse en esprit d'épreuve (type d'Angleterre) déterminées par l'hydromètre de Sikes. Revised and edited by J. DUJARDIN. Paris 1909. pp. 15. ill.

RUBBER DEVELOPMENTS. *See* BRITISH RUBBER DEVELOPMENT BOARD.

RUBBER RESEARCH INSTITUTE OF MALAYA. Planting Manual, No. 4. Latex preservation, concentration and shipment. 2nd edition. By J. H. PIDFORD. Kuala Lumpur 1947. pp. [iv] + 76.

RUSSELL, H. *See* YOST, D. M.

RYLE, J. A. *See* MEDICAL RESEARCH COUNCIL. Memorandum No. 18.

SAAL, R. N. J. *See* EILERS, H.

SAGARIN, E. *See* NAVES, Y. R.

SAHYUN, M. Proteins and amino acids in nutrition. New York 1948. pp. xvi + 566. ill.

SALLERON, J. *See* RUAU, L.

SANTOS RUIZ, A. Hormonas. Madrid 1940. pp. 328. ill.

—— Vitaminas. Historia—Nomenclatura—Clasificación—Función—Obtención—Química—Propriedades—Síntesis—Valoración Unidades—Distribución—Relaciones. Madrid 1941. pp. xiv + 294. ill.

—— Fermentos. Clasificación, función, distribución, obtención, constitución, propriedades, valoración. Madrid 1944. pp. xx + 392. ill.

—— Bioquímica de los elementos. (Monografías de Ciencia Moderna, No. 7.) [Madrid] 1945. pp. 111.

SANTOS RUIZ, A., and ROTLLANT DE FRANCH, M. Vitaminas y hormonas. Relaciones entre constitución química y acción biológica : relaciones entre sí. Madrid 1943. pp. 143.

SATTERFIELD, G. H. *See* BIOLOGICAL SYMPOSIA. Vol. XII.

SAUCHELLI, V. Manual on fertilizer manufacture. Baltimore 1946. pp. 126. ill.

SCHENK, M. Werkstoff Aluminium und seine anodische Oxydation; ein Handbuch und Ratgeber für den Praktiker. Bern 1948. pp. 1042. ill.

SCHIMMEL & Co. Semi-Annual report on essential oils, synthetic perfumes, etc. 11 vols. Leipzig 1890—96. (*Reference.*)

SCHMIDT, H. *See* FIAT REVIEW OF GERMAN SCIENCE, 1939—46.

SCHWARZKOPF, P. [and others]. Powder metallurgy; its physics and production. New York 1947. pp. xii + 379. ill.

SCOTTISH SEAWEED RESEARCH ASSOCIATION. Annual Report for 1946, etc. Edinburgh [1947 +]. (*Reference.*)

SEITZ, F. *See* AMERICAN PHYSICAL SOCIETY. *Division of Electron Optics.*

SENENT PÉREZ, S. Estado metálico y estado sólido segun la química física moderna. (Monografías de Ciencia Moderna, No. 1.) [Madrid] 1945. pp. 94. ill.

SHAND, S. J. Eruptive rocks, their genesis, composition, classification, and their relation to ore-deposits, with a chapter on meteorites. 3rd edition. London 1947. pp. xvi + 488. ill.

SHERMAN, H. C. Calcium and phosphorus in foods and nutrition. New York 1947. pp. vi + 176. ill.

SHRINER, R. L., and FUSON, R. C. The systematic identification of organic compounds; a laboratory manual. 3rd edition. New York 1948. pp. ix + 370. ill.

SILLIMAN, B. *See* FULTON, J. F.

SILMAN, H. Chemical and electro-plated finishes. The protective treatment of metals. London 1948. pp. xiii + 414. ill.

SIMPSON, B. W. *See* MEDICAL RESEARCH COUNCIL. Memorandum No. 18.

SIMPSON, S. G. *See* HAMILTON, L. F.

SMITH, E. A. A manual on dental metallurgy and non-metallic materials. 6th edition. London 1947. pp. viii + 391. ill.

SMITH, E. B. *See* OLLARD, E. A.

SMITH, M. D. *See* BRITISH NON-FERROUS METALS RESEARCH ASSOCIATION. *Research Reports.*

SMITH, P. W. P. *See* CANADA, DOMINION OF. *National Research Council.*

SNELL, C. T. *See* SNELL, F. D.

SNELL, F. D., and SNELL, C. T. Colorimetric methods of analysis, including some turbidimetric and nephelometric methods. 3rd edition. Vol. I. Theory —instruments—pH. New York 1948. pp. xii + 239. ill.

SOCIETY FOR EXPERIMENTAL BIOLOGY. *Symposia.* No. 1. Nucleic acid. Cambridge 1947. pp. vii + 290. ill. (*Reference.*)

SOCIETY OF PUBLIC ANALYSTS AND OTHER ANALYTICAL CHEMISTS. *Physical Methods Group* and *Biological Methods Group.* Symposium on methods of penicillin assay; their purpose, scope and validity. Cambridge 1948. pp. iv + 34. ill.

SOMMER, A. Photoelectric cells. London 1946. pp. viii + 104. ill.

SQUIRE, A. Powder metallurgy: a report of the Watertown Arsenal Laboratory. Brooklyn, N.Y. 1947. pp. [184]. ill. [Photo-Offset.]

STAUDINGER, H. Makromolekulare Chemie und Biologie. Basel 1947. pp. xiii + 160. ill. (Two copies.)

STEVELS, J. M. Progress in the theory of the physical properties of glass. Amsterdam 1948. pp. xii + 104. ill.

STEVENSON, A. E. *See* NATIONAL CANNERS' ASSOCIATION. *Research Laboratory.*

STEVENSON, W. F. The composition of hydrogen and the non-decomposition of water incontrovertibly established, in answer to the award of a medal by the Royal Society, whereby the contrary doctrines are absolutely affirmed. Also the absurdity of the existing systems of electricity and magnetism demonstrated, and the true ones given. 2nd edition. London 1849. pp. 156.

SUGAR RESEARCH FOUNDATION, INC. Scientific Report Series, No. 6. Bacterial polysaccharides. By T. H. EVANS and H. HIBBERT. New York 1947. pp. [iv] + 32.

—— —— No. 9. The taste sense and the relative sweetness of sugars and other sweet substances. By A. T. CAMERON. New York 1947. pp. [viii] + 72. ill.

—— —— No. 10. Chromatography of sugars and related substances. By W. W. BINKLEY and M. L. WOLFROM. New York 1948. pp. [vi] + 34. ill.

—— Technological Report Series No. 3. Wax and fatty by-products from sugarcane. By R. T. BALCH. New York 1947. pp. [viii] + 62.

—— —— No. 4. Use of molasses in grass silage preparation. By C. B. BENDER. New York 1948. pp. [vi] + 22.

—— The Sugar Molecule. Vol. I, etc. New York 1947 +. (*Reference.*)

SURUGUE, J. [Editor.] Techniques générales du laboratoire de physique. Vol. I. Paris 1947. pp. 433. ill.

SWANEY, M. W. *See* ELLIS, C.

TEXTILE FOUNDATION. *See* TEXTILE RESEARCH INSTITUTE.

TEXTILE RESEARCH INSTITUTE and TEXTILE FOUNDATION. Textile Research Journal, Vol. 17, etc. New York 1947 +. (*Reference.*)

TEXTILE RESEARCH JOURNAL. *See* TEXTILE RESEARCH INSTITUTE.

THEILHEIMER, W. Synthetic methods of organic chemistry; a thesaurus. Vol. 1, 1942—44. Translated from the German by H. WYNBERG. New York 1948. pp. x + 254. (*Reference.*)

THOMAS, M. Plant physiology. 3rd edition. London 1947. pp. xi + 504. ill.

THOMSON, E. H. *See* FULTON, J. F.

THOMSON, R. D. Notes of lectures. 1828—29. [MS.] (*Reference.*)

THORNE, P. C. L. *See* EPHRAIM, F.

THRELFALL, R. E. Glass tubing. London 1946. pp. 36. ill. (Two copies.)

TIN RESEARCH INSTITUTE. The spectrographic analysis of tin and tin–lead solders. Greenford 1948. pp. 31. ill.

TOLANSKY, S. Hyperfine structure in line spectra and nuclear spin. 2nd edition. London 1948. pp. viii + 120. ill.

TOMEO, M. Las resinas. Barcelona 1939. pp. vii + 527. ill.

TOWNSEND, SIR JOHN. Electrons in gases. London 1947. pp. viii + 166. ill.

TRELEASE, S. F. The scientific paper; how to prepare it, how to write it. Baltimore 1947. pp. xii + 152. ill.

TROTMAN, E. R. *See* TROTMAN, S. R.

TROTMAN, S. R., and TROTMAN, E. R. Textile analysis. 2nd edition. London 1948. pp. [vi] + 303. ill.

TSWETT, M. S. Chromatographic adsorption analysis. Selected papers. Edited by A. A. RICHTER and T. A. KRASNOSSELSKAJA. [Moscow.] 1946. pp. 272. ill. [In Russian.]

TURTLE, E. E. *See* MINISTRY OF FOOD.

TYLER, C. Chemical engineering economics. 3rd edition. New York 1948. pp. x + 321. ill.

UHLIG, H. H. *See* ELECTROCHEMICAL SOCIETY.

UNION OF SOCIALIST SOVIET REPUBLICS. *Institute of Organic Chemistry.* Synthetic methods in relation to organometallic compounds. Edited by A. N. NESMEYANOV and K. A. KOCHESHKOV. No. 5. Synthetic methods in relation to organometallic compounds of elements of the 4th group. Moscow 1947. pp. 129. [In Russian.]

UNITED STATES PHARMACOPŒIAL CONVENTION. The pharmacopœia of the United States of America. 13th revision. Easton, Pa. 1947. pp. cvii + 957. (*Reference.*)

UNIVERSIDAD NACIONAL DE CUYO. *Instituto del Petroleo.* Publícacion No. 1. El uranio en petróleo, asfaltitas y esquistos. By S. G. LEXOW and E. P. P. MANESCHI. Mendoza 1948. pp. 11.

VERWEY, E. J. W., and OVERBEEK, J. TH. G. Theory of the stability of lyophobic colloids; the interaction of sol particles having an electric double layer. New York 1948. pp. xii + 205. ill.

VILBRANDT, F. C. Chemical engineering plant design. New York 1934. pp. x + 341. ill.

VOGEL, A. I. A text-book of practical organic chemistry, including qualitative organic analysis. London 1948. pp. xxiii + 1012. ill.

WAARDEN, M. VAN DER. *See* EILERS, H.

WALDEN, P. Geschichte der Chemie. Bonn 1947. pp. 116.

WALLERSTEIN LABORATORIES. Bottle beer quality. A 10-year research record. New York 1948. pp. iii + 161. ill.

WALLIS, T. E. Practical pharmacognosy. 5th edition. London 1948. pp. ix + 230. ill.

WARTH, A. H. The chemistry and technology of waxes. New York 1947. pp. viii + 519. ill.

WASHINGTON, UNIVERSITY OF. Publications in Fisheries. Bacteriological investigations on raw salmon spoilage. By C. R. FELLERS. Seattle 1926. pp. 36.

—— —— Fish preservation by hypochlorites. By T. PAI CHEN and C. R. FELLERS. Seattle 1926. pp. 23. ill.

WASHINGTON, UNIVERSITY OF. Publications in Fisheries. Iodine content of the Pacific Coast salmon. By N. D. JARVIS, R. W. CLOUGH, and E. D. CLARK. Seattle 1926. pp. 29.

—— —— Preserved pickled herring. By C. L. ANDERSON. Seattle 1925. pp. 60.

WATER AND SEWAGE WORKS. Vol. 95, No. 6, etc. Chicago 1946 +. (*Reference.*)

WEBER, H., and BECHLER, H. Über den Zerfall der bituminösen Strassenbau-Emulsionen durch Berührung mit dem Gestein. Berlin 1932. pp. 90. ill.

WEIL, B. H., and LANE, J. C. Synthetic petroleum from the Synthine process. Brooklyn 1948. pp. xi + 303. ill.

WEINSTEIN, J. J. *See* WHITE, C. S.

WEPSTER, B. M. Onderzoekingen over sterische beïnvloeding van mesomerie. Dordrecht 1947. pp. 110.

WERTH, A. VAN DER. Neue Sulfonierungsverfahren zur Herstellung von Dispergier-, Netz-, und Waschmitteln. Berlin 1932. pp. 66.

WESTERN AUSTRALIA. *Department of Agriculture.* The examination of the Western Australian poison plants. 1st Progress Report: 2nd and 3rd Progress Reports, by E. A. MANN. Perth 1906. pp. 14, 11. ill.

WEST VIRGINIA PULP AND PAPER CO. *Industrial Chemical Sales Division.* Taste and odor control in water purification. New York 1947. pp. [iv] + 164. ill.

WEYGAND, C. *See* HAND- UND JAHRBUCH DER CHEMISCHEN PHYSIK. II. Part 3c.

WHITE, C. S., and WEINSTEIN, J. J. Blood derivatives and substitutes; preparation, storage, administration and clinical results, including a discussion of shock; etiology, physiology, pathology and management. Baltimore 1947. pp. xviii + 484. ill.

WILKINSON, W. P. European regional appellations considered in the light of International Conventions and Treaties as improper descriptions for Australian wines. Melbourne 1919. pp. 12.

WILLIAMS, G. E. Technical literature, its preparation and presentation. London 1948. pp. 117.

WILLIAMS, H. E. Cyanogen compounds: their chemistry, detection and estimation. 2nd edition. London 1948. pp. xvi + 443.

WILLIAMS, R. T. Detoxication mechanisms: the metabolism of drugs and allied organic compounds. London 1947. pp. viii + 288.

WILLIAMSON, G. *See* LINTON, R. G.

WILSON, D. C. *See* MEDICAL RESEARCH COUNCIL. Memorandum No. 18.

WIRTH, M. M. Bicyclische Verbindungen mit einem vielgliedrigen Ring. Zürich 1948. pp. 54. ill.

WOLFROM, M. L. *See* SUGAR RESEARCH FOUNDATION, INC. Scientific Report Series, No. 10.

WYNBERG, H. *See* THEILHEIMER, W.

YARWOOD, J. High vacuum technique: theory, practice, industrial applications, and properties of

materials. 2nd edition. London 1948. pp. viii + 140. ill.

YOST, D. M., RUSSELL, H., and GARNER, C. S. The rare-earth elements and their compounds. New York 1947. pp. ix + 92. ill.

ZADE, H. P. *See* HAIM, G.

ZEERLEDER, A. VON. Technologie der Leichtmetalle. Zürich 1947. pp. xii + 364. ill.

ZINC DEVELOPMENT ASSOCIATION. Z.D.A. Abstracts; a review of recent technical literature on the various uses of zinc and its products. Vol. 6, No. 7, etc. Oxford 1948 +. (*Reference.*)

PRINTED IN GREAT BRITAIN BY RICHARD CLAY AND COMPANY, LTD.,
BUNGAY, SUFFOLK.

1948

JOURNAL OF THE CHEMICAL SOCIETY

TITLE-PAGES AND INDEXES

1948

LONDON: THE CHEMICAL SOCIETY

PRINTED IN GREAT BRITAIN BY RICHARD CLAY AND COMPANY, LTD., BUNGAY, SUFFOLK.

THE CHEMICAL SOCIETY

Patron:
HIS MAJESTY THE KING.

President:
SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.S.

Vice-Presidents:
WHO HAVE FILLED THE OFFICE OF PRESIDENT:

F. G. DONNAN, C.B.E., D.Sc., LL.D., F.R.S.
SIR NORMAN HAWORTH, Sc.D., LL.D., F.R.S.
SIR CYRIL HINSHELWOOD, M.A., Sc.D., D.Sc., F.R.S.
W. H. MILLS, M.A., Sc.D., F.R.S.
SIR ROBERT ROBINSON, M.A., D.Sc., LL.D., P.R.S.
N. V. SIDGWICK, C.B.E., D.Sc., LL.D., F.R.S.

Vice-Presidents:

R. P. BELL, M.A., B.Sc., F.R.S.
G. M. BENNETT, C.B., M.A., Sc.D., F.R.S., F.R.I.C.
J. KENYON, D.Sc., F.R.S., F.R.I.C.
R. P. LINSTEAD, C.B.E., M.A., PH.D., D.Sc., F.R.S.
S. SUGDEN, D.Sc., F.R.S., F.R.I.C.
A. R. TODD, M.A., D.PHIL., D.Sc., F.R.S.

Treasurer:
SIR WALLACE AKERS, C.B.E., B.A., F.R.I.C.

Secretaries:
SIR JOHN SIMONSEN, D.Sc., F.R.S., F.R.I.C. D. H. HEY, PH.D., D.Sc., F.R.I.C.
A. KING, C.B.E., D.Sc., A.R.C.S.

Ordinary Members of Council:

L. L. BIRCUMSHAW, M.A., D.Sc.
G. R. CLEMO, D.PHIL., D.Sc., PH.D., F.R.S.
A. H. COOK, PH.D., D.Sc., F.R.I.C., D.I.C.
F. S. DAINTON, M.A., PH.D.
J. F. J. DIPPY, PH.D., D.Sc., F.R.I.C.
G. M. DYSON, M.A., PH.D., B.Sc., F.R.I.C.
A. E. GILLAM, D.Sc., F.R.I.C.
F. R. GOSS, D.Sc., PH.D., A.R.C.S., F.R.I.C.
FRANCES M. HAMER, M.A., Sc.D., D.Sc., F.R.I.C.
S. H. HARPER, D.Sc., PH.D., A.R.C.S.
D. W. HILL, PH.D., D.Sc., F.R.I.C.
A. McGOOKIN, D.Sc., PH.D., A.R.I.C.
T. MALKIN, PH.D., D.Sc., F.R.I.C.
F. G. MANN, Sc.D., D.Sc., F.R.S., F.R.I.C.
H. W. MELVILLE, PH.D., D.Sc., F.R.S.
E. G. V. PERCIVAL, PH.D., D.Sc., F.R.I.C.
H. N. RYDON, D.Sc., PH.D., D.PHIL., A.R.C.S., F.R.I.C.
F. S. SPRING, PH.D., D.Sc., F.R.I.C.
L. E. SUTTON, M.A., D.PHIL.
J. WALKER, Ph.D., D.PHIL., D.Sc.
T. S. WHEELER, PH.D., D.Sc., F.R.I.C., M.I.CHEM.E.

Ex-officio Members of Council:

H. E. COX, D.Sc., PH.D., F.R.I.C. (Chairman of the Joint Library Committee).
L. H. LAMPITT, D.Sc., F.R.I.C. (Chairman of the Bureau of Abstracts).
E. K. RIDEAL, M.B.E., M.A., D.Sc., PH.D., F.R.S. (Chairman of the Chemical Council).

General Secretary:
J. R. RUCK KEENE, M.B.E., B.A.

Editor:
J. E. DRIVER, M.A., Ph.D., M.Sc., F.R.I.C.

Librarian:
A. E. CUMMINS.

Assistant Editors:
A. D. MITCHELL, D.Sc., F.R.I.C.
L. C. CROSS, PH.D., A.R.C.S., F.R.I.C.

Indexer:
MARGARET LE PLA, B.Sc.

INDEX OF AUTHORS, 1948.

A.

Acheson, *R. M.* See **King,** *F. E.*

Addison, *C. C.*, **Bagot,** *J.*, and **McCauley,** *H. S.*, the properties of freshly-formed surfaces. Part VIII. Expansion of soluble films of decoic acid at the air–water interface, 936.

Addison, *C. C.*, and **Hutchinson,** *S. K.*, the properties of freshly-formed surfaces. Part VII. The application of the vertical-plate technique to the study of soluble films at air–liquid and liquid–liquid interfaces. Part IX. Expansion of soluble films of sodium dodecyl sulphate at air–water and toluene–water interfaces, 930, 943.

Albert, *A.*, acridine syntheses and reactions. Part IV. A new synthesis of aminoacridines from formic acid and diarylamines, 1225.

Albert, *A.*, **Brown,** *D. J.*, and **Duewell,** *H.*, some syntheses in the benzquinoline, benzacridine, and phenanthridine series, 1284.

Albert, *A.*, **Goldacre,** *R.*, and **Phillips,** *J.*, the strength of heterocyclic bases, 2240.

Anderson, *J. S.* See **Bevan,** *D. J. M.*

Anker, *R. M.*, and **Cook,** *A. H.*, experiments in the piperidine series. Part IV., 806.

Armstrong, *G. P.*, **Grove,** (*Miss*) *D. H.*, **Hammick,** *D. L.*, and **Thompson,** *H. W.*, some catalysed gas-phase reactions of aromatic hydrocarbons. Part III. The methylation of naphthalene by means of dimethyl ether, 1700.

Arrol, *W. J.*, and **Glascock,** *R.*, the conversion of carbon dioxide into acetylene on the scale of 2—20 micromoles, 1534.

Ashdown, *A.*, and **Kletz,** *T. A.*, the infra-red spectra of mixtures of aldehydes and alcohols, 1454.

Ashley, *J. N.*, **Grove,** *J. F.*, and **Henshall,** *T.*, attempts to find new chemotherapeutic amidines. Part IX. Derivatives of 1 : 1-diphenylethylene and naphthalene, 261.

Ashworth, *R. deB.*, symmetrically disubstituted formamidines; formation by Raney-nickel reduction of thioureas, 1716.

Ashworth, *R. de B.*, **Crowther,** *A. F.*, **Curd,** *F. H. S.*, and **Rose,** *F. L.*, synthetic antimalarials. Part XXIV. Some 2-phenylureido- and 2-phenylthioureido-4-dialkylaminoalkylamino-6-methylpyrimidines, 581.

Asperger, *S.* See **Weber,** *K.*

Asquith, *R. S.*, **Hammick,** *D. L.*, and **Williams,** *P. L.*, the conversion of mepacrine and similar derivatives of 5-aminoacridines into thioacridones by the action of hydrogen sulphide, 1181.

Aston, *F. W.*, obituary notice of, 1468.

Atherton, *F. R.*, **Howard,** *H. T.*, and **Todd,** *A. R.*, studies on phosphorylation. Part IV. Further studies on the use of dibenzyl chlorophosphonate and the examination of certain alternative phosphorylation methods, 1106.

Attenburrow, *J.*, **Elliott,** *D. F.*, and **Penny,** *G. F.*, a new synthesis of DL-threonine, 310.

B.

Backhouse, *T.*, **McGookin,** *A.*, **Matchet,** *J.*, **Robertson,** *Alexander*, and **Tittensor,** *E.*, rottlerin. Part VII. The synthesis of tetrahydrorottlerin and of tetrahydro*allo*-rottlerin and the reversibility of the rottlerone change, 113.

Baddar, *F. G.*, 2-methoxy*meso*benzanthrone, 1088.

Baddar, *F. G.*, and **El-Assal,** *L. S.*, phenylpropiolic acids. Part II. The dimerisation of *p*-nitro- and *p*-methoxyphenylpropiolic acid, 1267.

Baddar, *F. G.*, **El-Assal,** *L. S.*, and **Gindy,** *M.*, 1-phenylnaphthalenes. Part I. The synthesis of 2′ : 5-dimethoxy-1-phenyl-, 4′ : 7-dimethoxy-1-phenyl-, and 1-*p*-tolyl-7-methylnaphthalene-2 : 3-dicarboxylic acids, 1270.

Baddar, *F. G.*, and **Gindy,** *M.*, 3 : 4-benzfluorenones. Part II. Further observations on the effect of groups on their fission with alkali, 1231.

Badger, *G. M.*, a modified synthesis of chrysene, 999.

polycyclic aromatic amines. Part I., 1756.

Badger, *G. M.*, **Cook,** *J. W.*, and **Walker,** *T.*, synthesis of piperidine derivatives. Part II. Aryldecahydroquinolines, 2011.

Bagot, *J.* See **Addison,** *C. C.*

Bailey, *A. S.*, and **Robinson,** (*Sir*) *R.*, strychnine and brucine. Part XLIX. A new method for the preparation of pseudostrychnine, 703.

Bailey, *D.* See **Hodgson,** *H. H.*

Baker, *J. W.*, α-methylenic reactivity in olefinic systems. Part III. The Prins reaction with ethylene and α-methylstyrene, 89.

Baker, *K.*, 4-aminocinnoline, 1713.

Baker, *W.*, and **Brown,** *N. C.*, the Elbs persulphate oxidation of phenols, and its adaptation to the preparation of monoalkyl ethers of quinols, 2303.

Baker, *W.*, and **Flemons,** *G. F.*, dimerides of anethole, 1984.

the structure of ginkgetin. Part I. Synthesis of 5 : 8-dihydroxy-4′-methoxyflavone, 2138.

Baker, *W.*, and **Leeds,** *W. G.*, attempts to prepare new aromatic systems. Part I. *cyclo*Pentindene, phenyl*cyclo*pentanecarboxylic acids, and derived ketones, 974.

Balaban, *I. E.*, and **Levy,** *M. B.*, 1 : 1 : 1-trichloro-2 : 2-di-(*p*-aminophenyl)ethane, 1458.

Baly, *E. C. C.*, obituary notice of, 1721.

Banks, *A. A.*, **Emeléus,** *H. J.*, **Hazeldine,** *R. N.*, and **Kerrigan,** *V.*, the reaction of bromine trifluoride and iodine pentafluoride with carbon tetrachloride, tetrabromide, and tetraiodide and with tetraiodoethylene, 2188.

Bannister, *B.*, and **Plant,** *S. G. P.*, the action of nitric acid on polycyclic indole derivatives. Part XIV. Acenaphtheleno(7′ : 8′ : 2 : 3)indole, 1247.

Barakat, *M. Z.* See **Schönberg,** *A.*

Barany, *H. C.* See **Pianka,** *M.*

Barber, *H. J.*, and **Wragg,** *W. R.*, a convenient laboratory preparation of anhydrous hydrazine, 1458.

Barker, *G. R.*, the chemistry of ribose and its derivatives. Part I. Methyl-*d*-ribofuranoside and the characterisation of trimethyl *d*-ribofuranose, 2035.

Barker, (*Mrs.*) *M.*, **Hunter,** *L.*, and **Reynolds,** *N. G.*, the associating effect of the hydrogen atom. Part XIII. The N–H–O bond; esters of carbonic acid, 874.

Barltrop, *J. A.*, and **Nicholson,** *J. S.*, the oxidation products of phenols. Part I. The structure of purpurogallin, 116.

Barrer, *R. M.*, synthesis of a zeolitic mineral with chabazite-like sorptive properties, 127.

syntheses and reactions of mordenite, 2158.

Barrer, *R. M.*, and **Riley,** *D. W.*, sorptive and molecular-sieve properties of a new zeolitic mineral, 133.

Barrowcliff, *M.*, obituary notice of, 1475.

Barton, *D. H. R.*, interactions between non-bonded atoms, and the structure of *cis*-decalin, 340.

Barton, *D. H. R.*, and **Cox,** *J. D.*, the application of the method of molecular rotation differences to steroids. Part IV. Optical anomalies. Part V. Olefinic unsaturation at the 7 : 8-position. Part VI. *neo*Sterol, 783, 1354, 1357.

Barton, *D. H. R.*, and **Schmeidler,** *G. A.*, the application of the method of electrostatic energy differences. Part I. Stereochemistry of the diterpenoid resin acids, 1197.

Bashford, *V. G.*, and **Wiggins,** *L. F.*, anhydrides of polyhydric alcohols. Part X. The conversion of glucamine into 1 : 4-anhydrosorbitol; the constitution of benzylidene 1 : 4-anhydrosorbitol, 299.

Batt, *R. F.*, and **Woodcock,** *D.*, the condensation of chloral with aryl cyanides, 2322.

Baxter, *R. A.*, **McLean,** *A. C.*, and **Spring,** *F. S.*, application of the Hofmann reaction to the synthesis of heterocyclic compounds. Part V. The synthesis of 9-D-mannopyranosidoxanthine and of 9-D-ribopyranosidoxanthine, 523.

Baxter, *R. A.*, **Newbold,** *G. T.*, and **Spring,** *F. S.*, pyrazine derivatives. Part VI. The oxidation of 2-ethoxy- and 2-chloro-pyrazine derivatives with hydrogen peroxide, 1859.

Beech, *W. F.*, preparation of certain nuclear-substituted 2-aminophenolsulphonic acids, 212.

Beer, *R. J. S.*, **Clarke,** *K.*, **Khorana,** *H. G.*, and **Robertson,** *Alexander*, the chemistry of bacteria. Part I. The synthesis of hydroxyindoles, 1605.

the chemistry of the melanins. Part I. The synthesis of 5 : 6-dihydroxyindole and related compounds, 2223.

Bell, *D. J.*, applications of periodate oxidation to some problems of carbohydrate chemistry, 992.

Bell, *F.*, and **Waring,** *D. H.*, stilbenecarboxylic acids, 1024.

Bell, *R. P.*, and **Tantram,** *A. D. S.*, acid–base catalysis in non-aqueous solvents. Part XI. The halogenation of acetone by various *N*-halogen compounds in chlorobenzene solution at 50°, 370.

Bergmann, *E.*, the bromination of 1 : 5-dihydroxynaphthalene and its methyl ethers, 1283.

Best, *A. P.*, **Ingold,** *C. K.*, and **Wilson,** *C. L.*, excited states of benzene. Part VII. Description and analysis of the first ultraviolet band system of the fluorescence spectrum of 1 : 3 : 5-trideuterobenzene, 456.

Bevan, *D. J. M.*, **Shelton,** *J. P.*, and **Anderson,** *J. S.*, properties of some simple oxides and spinels at high temperatures, 1729.

Bevington, *J. C.*, and **Norrish,** *R. G. W.*, the cross-linking of vinyl polymers by Friedel–Crafts catalysts. Part I., 771.

Bick, *I. R. C.*, and **Todd,** *A. R.*, alkaloids of *Daphnandra* species. Part I. Repandine, 2170.

Bide, *A. E.*, **Henbest,** *H. B.*, **Jones,** *E. R. H.*, **Peevers,** *R. W.*, and **Wilkinson,** *P. A.*, studies in the sterol group. Part XLVII. A new route to 7-dehydrocholesterol (provitamin D_3) and its derivatives, 1783.

Bide, *A. E.*, **Henbest,** *H. B.*, **Jones,** *E. R. H.*, and **Wilkinson,** *P. A.*, studies in the sterol group. Part XLVIII. 7-Substituted cholesterol derivatives and their stereochemistry (Part I). 7-Halogeno-derivatives, 1788.

Billett, *F.* See **Morrison,** *T. J.*

Bircumshaw, *L. L.*, and **Harris,** *I.*, the thermal decomposition of lead oxalate, 1898.

Birtwell, *S.*, **Curd,** *F. H. S.*, **Hendry,** *J. A.*, and **Rose,** *F. L.*, synthetic antimalarials. Part XXX. Some N^1-aryl-N^4 : N^5-dialkyldiguanides and observations on the conversion of guanylthioureas into diguanides, 1645.

Blayden, *H. E.*, **Gibson,** *J.*, and **Riley,** *H. L.*, a study of bituminous coal by (*a*) exhaustive solvent extraction, and (*b*) *X*-ray diffraction, 1693.

Bobtelsky, *M.*, and **Glasner,** *A.*, the oxidation of hydrobromic acid by chromic acid in the presence of manganous sulphate, 1376.

Bourne, *E. J.*, **Donnison,** *G. H.*, **Haworth,** (*Sir*) *N.*, and **Peat,** *S.*, thymol and *cyclo*hexanol as fractionating agents for starch, 1687.

Bourne, *E. J.*, **Haworth,** (*Sir*) *N.*, **Macey,** *A.*, and **Peat,** *S.*, the amylolytic degradation of starch; a revision of the hypothesis of sensitisation, 924.

Bourne, *E. J.*, and **Wiggins,** *L. F.*, ethylidene derivatives of sorbitol, 1933.

Boyd, *J.*, and **Robertson,** *Alexander*, the chemistry of the "insoluble red" woods. Part II. A new synthesis of 4-hydroxycoumarins, 174.

Bradfield, *A. E.*, and **Penney,** (*Miss*) *M.*, the catechins of green tea. Part II., 2249.

Bradley, *W.*, cationoid reactivity of aromatic compounds. Part VI. The direct amination of *meso*benzanthrone, 1175.

Bradley, *W.*, and **Jadhav,** *G. V.*, cationoid reactivity of aromatic compounds. Part VII. The composition of the di*meso*benzanthronyl formed by the action of alkaline condensing agents on *meso*benzanthrone. Part VIII. The action of fused potassium hydroxide on 6 : 6′-di*meso*benzanthronyl and a note on the properties of 6- and 8-chloro*meso*benzanthrones, 1622, 1746.

Braude, *E. A.*, the kinetics of anionotropic rearrangement. Part VII. The simultaneous rearrangement and hydrolysis of propenylethynylcarbinyl acetate; general discussion of the mechanism of anionotropy and a comparison of the mobility of the hydroxyl and the acetoxyl group, 794.

acidity functions. Part I. Dissociation of hydrogen chloride in, and proton affinities of, some oxygen-containing solvents, 1971.

Braude, *E. A.*, and **Stern,** *E. S.*, acidity functions. Part II. The nature of hydrogen ion in some aqueous and non-aqueous solvents; the exceptional solvating properties of water, 1976.

the kinetics of anionotropic rearrangement. Part VIII. Medium composition, acidity function, and reaction rate, 1982.

Bridge, *W.*, **Coleman,** *F.*, and **Robertson,** *Alexander*, constituents of "*Cortex Piscidi Erythrinæ*." Part I. The structure of piscidic acid, 257.

Briggs, *L. H.*, and **Cawley,** *R. W.*, diterpenes. Part I. The identity of kaurene with podocarprene, 1888.

Briggs, *L. H.*, **Craw,** (*Miss*) *M. R.*, and **Dacre,** *J. C.*, chemistry of the *Coprosma* genus. Part II. The colouring matters from *Coprosma areolata*, 568.

Briggs, *L. H.*, and **Dacre,** *J. C.*, chemistry of the *Coprosma* genus. Part I. The colouring matters from *Coprosma australis*, 564.

Briggs, *L. H.*, **Dacre,** *J. C.*, and **Nicholls,** *G. A.*, chemistry of the *Coprosma* genus. Part III. A synthesis of areolatin and an isomer, 3 : 5 : 6 : 7-tetrahydroxy-2-methylanthraquinone, 990.

Briggs, *L. H.*, **Hassall,** *C. H.*, and **Taylor,** *W. I.*, a synthesis of leptospermone, 383.

Briggs, *L. H.*, and **Mangan,** *J. L.*, *Sophora* alkaloids. Part V. The alkaloids of the seeds of a possibly new species from Anawhata, New Zealand, 1889.

Briggs, *L. H.*, **Mangan,** *J. L.*, and **Russell,** *W. E.*, alkaloids of New Zealand *Senecio* species. Part I. The alkaloid from *Senecio kirkii*, 1891.

Brodrick, *C. I.*, **Peters,** *A. T.*, and **Rowe,** *F. M.*, a reaction of certain diazosulphonates derived from β-naphthol-1-sulphonic acid. Part XXV. The phthalazine reaction with bases not containing a nitro-group; derivatives of 2′-chlorobenzene-2-naphthol-1-diazosulphonate, 1026.

Brodrick, *C. I.* See also **Peters,** *A. T.*

Brown, *B. R.*, and **Hammick,** *D. L.*, a resolution of mepacrine [2-chloro-5-(δ-diethylamino-α-methylbutyl)amino-7-methoxyacridine], 99.

syntheses of some asymmetric naphthalene and acenaphthene hydrocarbons, 1395.

Brown, *D. J.* See **Albert,** *A.*

Brown, *D. M.*, and **Ross,** *W. C. J.*, the condensation of *p*-dimethylaminobenzaldehyde with 4-methylpyrimidine derivatives, 1715.

Brown, *F.*, **Halsall,** *T. G.*, **Hirst,** *E. L.*, and **Jones,** *J. K. N.*, the structure of starch; the ratio of non-terminal to terminal groups, 27.

Brown, *F.*, **Hirst,** *E. L.*, and **Jones,** *J. K. N.*, the structure of almond-tree gum. Part I. The constitution of the aldobionic acid derived from the gum, 1677.

Brown, *Fred*, and **Mann,** *F. G.*, the mechanism of indole formation from phenacylarylamines. Part II. The stability and reactions of phenacyl-*N*-alkylarylamines. Part III. The conditions and mechanism of the isomerisation and indolisation of phenacylarylamines, 847, 858.

Brown, *M. B.*, and **Kon,** *G. A. R.*, some heterocyclic analogues of stilbenes, 2147.

Brown, *N. C.* See **Baker,** *W.*

Brown, *R.*, and **Woodward,** *F. N.*, new organic sulphur vesicants. Part III. Homologues of 2 : 2′-di-(2-chloroethylthio)diethyl ether, 42.

Brownlie, *I. A.*, **Sutherland,** *G. B. B. M.*, and **Todd,** *A. R.*, infra-red spectroscopic measurements of substituted pyrimidines. Part I. The presence of hydrogen bonding in 4-triacetyl-*d*-xylosidaminopyrimidines, 2265.

Bruckner, *V.*, **Fodor,** *G.*, **Kiss,** *J.*, and **Kovács,** *J.*, synthesis of 6 : 7-diethoxy-3-methyl*iso*quinolines, 885.

Bruckner, *V.*, **Kovács,** *J.*, and **Koczka,** *I.*, occurrence of betulinic acid in the bark of the plane tree, 948.

Burton, *H.*, and **Davy,** *W. A.*, the synthesis of some aryl 2-thienyl sulphones and the nitration of thiophen-2-sulphonyl chloride, 525.

the use of phenylmagnesium bromide for the preparation of phenyl aryl sulphides, sulphoxides, and sulphones, 528.

Burton, *H.*, and **Hu,** *P. F.*, the synthesis of some *p*-arylsulphonylbenzaldehydes and related aldehydes and ketones, 602.

p-methylthiobenzenesulphonyl chloride and related compounds, 604.

Busha, *A.* See **Foster**, *R. T.*
Buu-Hoï, *N. P.*, and **Royer**, *R.*, the application of Pfitzinger reactions to the synthesis of quinoline derivatives; a novel route to 4-hydroxyquinolines, 106.
substitution reactions of triphenylethylene and its derivatives; a contribution to the problem of synthetic analogues of progesterone, 1078.
Byers, *A.*, and **Hickinbottom**, *W. J.*, reactions of unsaturated compounds. Part V. The action of organic per-acids on β-di*iso*butylene (2 : 4 : 4-trimethylpent-2-ene). Part VI. The reaction of α-di*iso*butylene with organic per-acids. Part VIII. The course of the oxidation of di*iso*butylene by chromic acid, 284, 1328, 1334.
Byrne, *G. T.*, obituary notice of, 253.

C.

Calderbank, *K. E.*, and **Le Fèvre**, *R. J. W.*, the dipole moments of benzocinnoline and benzocinnoline oxide in relation to those of *cis*-azo- and -azoxy-benzene, 1949.
Caldwell, *A. G.*, and **Walls**, *L. P.*, potential trypanocides of the *N*-heterocyclic series. Part I. Phenanthridinium salts, 188.
Campbell, *A. D.*, **Carter**, *C. L.*, and **Slater**, *S. N.*, the preparation of some branched-chain monocarboxylic acids, 1741.
Campbell, *N.*, and **McKail**, *J. E.*, the preparation of the halogenophenylacetic acids, 1251.
Campbell, *W. G.*, **Hirst**, *E. L.*, and **Jones**, *J. K. N.*, the ε-galactan of larch wood (*Larix decidua*), 774.
Capp, *C. W.*, **Cook**, *A. H.*, **Downer**, *J. D.*, and **Heilbron**, (*Sir*) *I.*, studies in the azole series. Part VIII. The interaction of α-amino-nitriles and carbethoxy*iso*thiocyanate, 1340.
Carrington, *H. C.*, the reaction between carbon disulphide and some α-methylamino-nitriles, 1619.
Carter, *C. L.* See **Campbell**, *A. D.*
Carter, *P. R.*, and **Hey**, *D. H.*, the action of chlorine on aqueous solutions of ammonium sulphinates, 147.
synthetic œstrogens of the triphenylethylene series, 150.
Carter, *P. R.*, **Hey**, *D. H.*, and **Morris**, *D. S.*, acyl derivatives of *p*-aminobenzenesulphonylguanidine, 143.
Catch, *J. R.*, **Elliott**, *D. F.*, **Hey**, *D. H.*, and **Jones**, *E. R. H.*, halogenated ketones. Part I. The bromination of acetone and methyl ethyl ketone. Part III. The preparation of bromomethyl ketones by the diazomethane reaction. Part IV. The application of the Friedel–Crafts reaction to the preparation of halogenated aliphatic ketones, 272, 278.
Catch, *J. R.*, **Hey**, *D. H.*, **Jones**, *E. R. H.*, and **Wilson**, *W.*, halogenated ketones. Part II. The bromination of methyl propyl and methyl *iso*propyl ketone, 276.
Catchpole, *A. G.*, and **Hughes**, *E. D.*, rearrangement and substitution in anionotropic systems. Part I. Test for bimolecular isomerisation in α-phenylallyl esters. Part II. Test for bimolecular rearrangement, and confirmation of the ionic mechanism of rearrangement, from product compositions in substitutions of α- and γ-methylallyl halides, 1, 4.
Catchpole, *A. G.*, **Hughes**, *E. D.*, and **Ingold**, *C. K.*, rearrangement and substitution in anionotropic systems. Part III. Mechanism of, and equilibrium in, anionotropic change, 8.
Cawley, *R. W.* See **Briggs**, *L. H.*
Cecil, *R.*, and **Ogston**, *A. G.*, the sedimentation of thymus nucleic acid in the ultracentrifuge, 1382.
Challenger, *F.*, and **Clapham**, *P. H.*, derivatives of 2 : 4 : 6-trinitrotoluene: (*a*) the nitration of polynitrostilbenes, (*b*) 2-(2 : 4 : 6-trinitrophenyl)ethyl alkyl (aryl) sulphides, 1612.
some derivatives of thionaphthen, 1615.
Challenger, *F.*, **Miller**, *S. A.*, and **Gibson**, *G. M.*, 2-thienyl- and 3-thienyl-thioacetic acids and their derivatives, 769.
Challenger, *F.*, and **Simpson**, (*Miss*) *M. I.*, studies on biological methylation. Part XII. A precursor of the dimethyl sulphide evolved by *Polysiphonia fastigiata*; dimethyl-2-carboxyethylsulphonium hydroxide and its salts, 1591.
Chapman, *N. B.*, and **Saunders**, *B. C.*, esters containing phosphorus. Part VI. Preparation of esters of fluorophosphonic acid by means of phosphorus oxydichlorofluoride, 1010.
Chard, *S. J.* See **Cullinane**, *N. M.*
Charlish, (*Mrs.*) *J. L.*, **Davies**, *W. H.*, and **Rose**, *J. D.*, reactions of α-cyanoprene (1-cyanobuta-1 : 3-diene). Part I. Addition of nitroparaffins. Part II. Addition of reactive methylene compounds, 227, 232.
Chatterjee, *R.*, **Cook**, *A. H.*, **Heilbron**, (*Sir*) *I.*, and **Levy**, *A. L.*, studies in the azole series. Part VII. A new route to α-amino-β-mercapto-acids, 1337.
Chaudhury, *D. N.*, **Holland**, *R. A.*, and **Robertson**, *Alexander*, syntheses of glycosides. Part XII. Fabiatrin, 1671.
Chaudhury, *D. N.*, **King**, *H. I.*, and **Robertson**, *Alexander*, syntheses of glycosides. Part XIII. Primulaverin, 2220.
Childs, *A. F.*, **Goldsworthy**, *L. J.*, **Harding**, *G. F.*, **King**, *F. E.*, **Nineham**, *A. W.*, **Norris**, *W. L.*, **Plant**, *S. G. P.*, **Selton**, *B.*, and **Tompsett**, *A. L. L.*, amines containing 2-halogenoethyl groups, 2174.
Childs, *A. F.*, and **Plant**, *S. G. P.*, some tri- and tetra-nitro-4-methyldiphenylamines, 1993.
Childs, *A. F.*, **Plant**, *S. G. P.*, **Tompsett**, *A. L. L.*, and **Weeks**, *G. A.*, compounds containing the 3-chloroallyl group, 2180.
Clapham, *P. H.* See **Challenger**, *F.*
Clarke, *J. R.*, **Glaser**, *G.*, and **Robertson**, *Alexander*, furano-compounds. Part VIII. The synthesis of *iso*visnagin and a partial synthesis of visnagin, 2260.
Clarke, *K.* See **Beer**, *R. J. S.*
Clarkson, *C. E.*, and **Malkin**, *T.*, an *X*-ray and thermal examination of the glycerides. Part IX. The polymorphism of simple triglycerides, 985.
Clemo, *G. R.*, and **Daglish**, *A. F.*, the synthesis of 1 : 3-dihydroxyphenazine, 2318.
Clemo, *G. R.*, and **King**, *T. J.*, strychnine. Part III. Some new reduction products, 1661.
Clemo, *G. R.*, and **Swan**, *G. A.*, the synthesis of derivatives of 4- and 5-azaindole, 198.
Cliffe, *W. H.*, **Curd**, *F. H. S.*, **Rose**, *F. L.*, and **Scott**, (*Miss*) *M.*, synthetic antimalarials. Part XXIII. 2-Arylguanidino-4-aminoalkylaminopyrimidines; further variations, 574.
Coates, *G. E.*, and **Sutton**, *L. E.*, the heats of formation of the —N=N— and >C=N— bonds, 1187.
Coleman, *F.* See **Bridge**, *W.*
Cook, *A. H.*, **Downer**, *J. D.*, and **Heilbron**, (*Sir*) *I.*, studies in the azole series. Part VI. The interaction of α-amino-nitriles and *iso*thiocyanates. Part IX. The interaction of α-amino-nitriles and alkyl *iso*thiocyanates, 1262, 2028.
Cook, *A. H.*, **Harris**, *G.*, and **Heilbron**, (*Sir*) *I.*, studies in the azole series. Part V. A synthesis of β-phenylcysteine, 1060.
Cook, *A. H.*, **Harris**, *G.*, **Heilbron**, (*Sir*) *I.*, and **Shaw**, *G.*, studies in the azole series. Part IV. The preparation of some thiazolones, 1060.
Cook, *A. H.*, **Heilbron**, (*Sir*) *I.*, and **Levy**, *A. L.*, studies in the azole series. Part III. The interaction of aminoacetonitrile and carbon disulphide, 201.
Cook, *A. H.*, **Heilbron**, (*Sir*) *I.*, and **Stern**, *E. S.*, studies in the azole series. Part X. Some 5-amino-2-mercapto-4-alkylthiazoles and 2 : 4-dithio-5-alkylhydantoins, 2031.
Cook, *A. H.* See also **Anker**, *R. M.*, **Capp**, *C. W.*, and **Chatterjee**, *R.*
Cook, *J. W.*, and **Philip**, *R.*, synthetic studies in the steroid series. Part I. Use of methyl γ-bromocrotonate in the synthesis of fused-ring hydroaromatic ketones, 162.
Cook, *J. W.*, **Philip**, *R.*, and **Somerville**, *A. R.*, azulenes. Part II. Exploration of new synthetic routes, 164.
Cook, *J. W.*, and **Schoental**, (*Miss*) *R.*, oxidation of carcinogenic hydrocarbons by osmium tetroxide, 170.
Cook, *J. W.* See also **Badger**, *G. M.*
Cooper, *K. A.*, **Dhar**, *M. L.*, **Hughes**, *E. D.*, **Ingold**, *C. K.*, **MacNulty**, *B. J.*, and **Woolf**, *L. I.*, mechanism of elimination reactions. Part VII. Solvent effects on rates and product-proportions in uni- and bi-molecular substitution and elimination reactions of alkyl halides and sulphonium salts in hydroxylic solvents, 2043.
Cooper, *K. A.*, **Hughes**, *E. D.*, **Ingold**, *C. K.*, and **MacNulty**, *B. J.*, mechanism of elimination reactions. Part VI. Introduction to a group of papers; unimolecular olefin formation from *tert.*-butyl- and *tert.*-amyl-sulphonium salts, 2038.
Cooper, *K. A.*, **Hughes**, *E. D.*, **Ingold**, *C. K.*, **Maw**, *G. A.*, and **MacNulty**, *B. J.*, mechanism of elimination reactions. Part VIII. Temperature effects on rates and product-proportions in uni- and bi-molecular substitution and elimination reactions of alkyl halides and sulphonium salts in hydroxylic solvents, 2049.

Cornforth, *J. W.*, and **Cornforth**, (*Mrs.*) *R. H.*, studies in the series of 4-substituted quinolines, 93.
Cornforth, *J. W.*, and **Huang**, *H. T.*, the condensation of benzamidine with α-diketones, 731.
"dibenzamidodioxytetrol," 1958.
further studies of oxazoles and glyoxalines, 1960.
experiments on a synthesis of penicillin, 1964.
synthesis of a 4-cyano-oxazole, 1969.
the action of hydrochloric acid on 5 : 5-dichloro-6-hydroxy-6-methyl-5 : 6-dihydrouracil, 1988.
Cornforth, (*Mrs.*) *R. H.* See **Cornforth**, *J. W.*
Cottrell, *T. L.*, binding energies in hydrocarbons, 1448.
Cottrell, *T. L.*, **Drake**, *G. W.*, **Levi**, *D. L.*, **Tully**, *K. J.*, and **Wolfenden**, *J. H.*, the thermochemistry of solutions. Part V. The heats of ionisation of some organic acids, 1016.
Cottrell, *T. L.*, and **Wolfenden**, *J. H.*, the thermochemistry of solutions. Part VI. The heat of ionisation of succinic acid, 1019.
Coulson, *C. A.* See **Crawford**, *V. A.*
Coulson, *E. A.*, and **Herington**, *E. F. G.*, remarks on Redlich's note on composition, pressure, and temperature relationships in binary azeotropic systems, 1987.
Cox, *J. D.* See **Barton**, *D. H. R.*
Craw, (*Miss*) *M. R.* See **Briggs**, *L. H.*
Crawford, *V. A.*, and **Coulson**, *C. A.*, the dimerisation of acenaphthylene, 1990.
Crowther, *A. F.*, **Curd**, *F. H. S.*, **Richardson**, (*Miss*) *D. N.*, and **Rose**, *F. L.*, synthetic antimalarials. Part XXIX. The preparation of some N^1-aryl-N^5-alkyl-N^5-alkyl- and dialkyldiguanides, 1636.
Crowther, *A. F.*, **Curd**, *F. H. S.*, and **Rose**, *F. L.*, synthetic antimalarials. Part XXV. Some 4-arylguanidino-2- and -6-dialkylaminoalkylaminopyrimidines, 586.
Crowther, *A. F.* See also **Ashworth**, *R. de B.*
Cullinane, *N. M.*, and **Chard**, *S. J.*, the action of methanol on naphthalene in the presence of catalysts of the alumina–silica type; formation of 2-methylnaphthalene, 804.
Cunneen, *J. I.*, and **Smith**, *F.*, the constitution of mesquite gum. Part I. Isolation of 6- and 4-glucuronosidogalactose. Part II. Methylated mesquite gum, 1141, 1146.
Curd, *F. H. S.*, **Graham**, *W.*, and **Rose**, *F. L.*, synthetic antimalarials. Part XXVI. Pyridyl- and pyrimidyl-aminopyrimidines, 594.
Curd, *F. H. S.*, **Hendry**, *J. A.*, **Kenny**, *T. S.*, **Murray**, *A. G.*, and **Rose**, *F. L.*, synthetic antimalarials. Part XXVIII. An alternative route to N^1-aryl-N^5-alkyldiguanides, 1630.
Curd, *F. H. S.*, **Hoggarth**, *E.*, **Landquist**, *J. K.*, and **Rose**, *F. L.*, synthetic antimalarials. Part XXXII. Some 4-arylamino- and 4-arylthio-2-aminoalkylaminoquinazolines, and 2-arylthio-4-aminoalkylaminoquinazolines, 1766.
Curd, *F. H. S.*, **Landquist**, *J. K.*, and **Rose**, *F. L.*, synthetic antimalarials. Part XXXI. 2-*p*-Chloroanilino-4-β-diethylaminoethylaminoquinazolines containing various substituents in the quinazoline nucleus, 1759.
Curd, *F. H. S.* See also **Ashworth**, *R. de B.*, **Birtwell**, *S.*, **Cliffe**, *W. H.*, and **Crowther**, *A. F.*
Cuthbertson, *W. W.*, and **Moffatt**, *J. S.*, contributions to the chemistry of synthetic antimalarials. Part VI. Some derivatives of 1 : 3 : 5-triazine, 561.
Cymerman, *J.*, **Koebner**, *A.*, and **Short**, *W. F.*, preparation of some *p*-alkylsulphonylbenzylammonium chlorides, 381.

D.

Dacre, *J. C.* See **Briggs**, *L. H.*
Daglish, *A. F.* See **Clemo**, *G. R.*
Danby, *C. J.* See **Partington**, *R. G.*, and **Rigby**, *H. A.*
Davey, *W.*, and **Latter**, *R. W.*, the preparation of symmetrical dinitrodiphenyls by the Ullmann reaction, 264.
Davies, *R. E.*, **Openshaw**, *H. T.*, **Spring**, *F. S.*, **Stanley**, *R. H.*, and **Todd**, *A. R.*, derivatives of arsacridine. Part II., 295.
Davies, *W. H.* See **Charlish**, (*Mrs.*) *J. L.*
Davoll, *J.*, **Lythgoe**, *B.*, and **Todd**, *A. R.*, experiments on the synthesis of purine nucleosides. Part XIX. A synthesis of adenosine. Part XX. A synthesis of guanosine, 967, 1685.
Davy, *W. A.* See **Burton**, *H.*
Dawson, *I. M.*, **Mathieson**, *A. McL.*, and **Robertson**, *J. M.*, the structure of certain polysulphides and sulphonyl sulphides. Part I. A preliminary *X*-ray survey, 322.
Dawson, *I. M.*, and **Robertson**, *J. M.*, the structure of certain polysulphides and sulphonyl sulphides. Part II. The crystal structure of 2 : 2′-di-iododiethyl trisulphide, 1256.
Dean, *F. M.*, and **Robertson**, *Alexander*, hydroxy-carbonyl compounds. Part XIII. Extensions of the Wolff rearrangement, 1674.
De la Mare, *P. B. D.*, **Hughes**, *E. D.*, and **Ingold**, *C. K.*, the modes of addition to conjugated unsaturated systems. Part IX. A discussion of mechanism and equilibrium, with a note on three-carbon prototropy, 17.
De la Mare, *P. B. D.*, and **Robertson**, *P. W.*, the kinetics of aromatic halogen substitution. Part IV. The 1-halogenonaphthalenes and related compounds, 100.
Demjén, *I.* See **Földi**, *Z.*
Desai, *R. L.* See **Rowe**, *F. M.*
Dewar, *M. J. S.*, the structure of ozone, 1299.
Dhar, *M. L.*, **Hughes**, *E. D.*, and **Ingold**, *C. K.*, mechanism of elimination reactions. Part X. Kinetics of olefin elimination from *iso*propyl, *sec.*-butyl, 2-*n*-amyl, and 3-*n*-amyl bromides in acidic and alkaline alcoholic media. Part XI. Kinetics of olefin elimination from *tert.*-butyl and *tert.*-amyl bromides in acidic and alkaline alcoholic media, 2058, 2065.
Dhar, *M. L.*, **Hughes**, *E. D.*, **Ingold**, *C. K.*, **Mandour**, *A. M. M.*, **Maw**, *G. A.*, and **Woolf**, *L. I.*, mechanism of elimination reactions. Part XVI. Constitutional influences in elimination; a general discussion, 2093.
Dhar, *M. L.*, **Hughes**, *E. D.*, **Ingold**, *C. K.*, and **Masterman**, *S.*, mechanism of elimination reactions. Part IX. Kinetics of olefin elimination from *n*-propyl, *n*-butyl, *n*-amyl, and *iso*butyl bromides in alkaline alcoholic media, 2055.
Dhar, *M. L.* See also **Cooper**, *K. A.*
Dixon, *S.* See **Hodgson**, *H. H.*
Dobson, *J.*, **Hutchison**, *W. C.*, and **Kermack**, *W. O.*, attempts to find new antimalarials. Part XXVII. Derivatives of various benzacridines and pyridoacridines, 123.
Dodgson, *D. P.* See **Hodgson**, *H. H.*
Donnison, *G. H.* See **Bourne**, *E. J.*
Dorée, *C.*, **McGhie**, *J. F.*, and **Kurzer**, *F.*, lanosterol. Part V. Hydrogenation of the inert double bond in lanosterol derivatives, 988.
Dostrovsky, *I.*, **Hughes**, *E. D.*, and **Ingold**, *C. K.*, the mechanism of substitution at a saturated carbon atom, 1283.
Downer, *J. D.* See **Capp**, *C. W.*, and **Cook**, *A. H.*
Drake, *G. W.* See **Cottrell**, *T. L.*
Drayton, *G. L.*, and **Thompson**, *H. W.*, the infra-red spectrum of keten, 1416.
Duewell, *H.* See **Albert**, *A.*
Duffin, *G. F.*, and **Kendall**, *J. D.*, the preparation of 4-hydroxyquinoline derivatives from aromatic amines and ethyl ethoxymethylenemalonate, 893.
Dyer, *B. S.*, obituary notice of, 896.

E.

Eade, *R. A.*, and **Earl**, *J. C.*, further studies on the sydnones, 2307.
Earl, *J. C.*, **Leake**, (*Miss*) *M. W.*, and **Le Fèvre**, *R. J. W.*, the dipole moments of *N*- and *C*-substituted sydnones, 2269.
Earl, *J. C.* See also **Eade**, *R. A.*
Edisbury, *J. R.*, **Hunter**, *R. F.*, and **Scott**, *A. D.*, the ultraviolet absorption spectra of some 2-aminobenzthiazole and 2-imino-3-methyl-2 : 3-dihydrobenzthiazole derivatives, 1497.
Edwards, *W. G. H.*, and **Petrow**, *V.*, some examples of the Schmidt rearrangement, 1713.
El-Assal, *L. S.* See **Badder**, *F. G.*
Elks, *J.*, **Hems**, *B. A.*, and **Ryman**, (*Miss*) *B. E.*, the synthesis of some α-amino-acids, 1386.
Elliott, *D. F.*, **Fuller**, *A. T.*, and **Harington**, (*Sir*) *C.*, bacteriostasis in the amino-acid series. Part I. Derivatives of alanine, 85.
Elliott, *D. F.* See also **Attenburrow**, *J.*, and **Catch**, *J. R.*
Elston, *C. H. R.*, **Peters**, *A. T.*, and **Rowe**, *F. M.*, halogenation of *m*-5- and *m*-2-xylenols; preparation and structure of certain polyhalogeno-*m*-5- and -*m*-2-xylenols, 367.
El Wakkad, *S. E. S.* See **Tourky**, *A. R.*
Emblem, *H. G.* See **McDowell**, *C. A.*
Emeléus, *H. J.*, **Maddock**, *A. G.*, **Miles**, *G. L.*, and **Sharpe**, *A. G.*, fluorides of the natural radioactive elements, 1991.

Emeléus, *H. J.*, and **Wood**, *J. F.*, the preparation and reactions of carbonyl and sulphuryl fluorides and chlorofluorides, 2183.
Emeléus, *H. J.* See also **Banks**, *A. A.*, and **Sharpe**, *A. G.*
Everett, *D. H.*, and **Pinsent**, *B. R. W.*, the relative strengths of some fatty acids, 1029.
Everett, *J. L.*, and **Kon**, *G. A. R.*, 1-phenyl-2-naphthyl- and 1 : 2-dinaphthyl-ethylenes, 1601.

F.

Fairbrother, *F.*, electrolytic dissociation processes. Part V. The solvolytic ionisation of molecular iodine, 1051.
Farthing, *A. C.* See **Parkes**, *G. D.*
Feachem, *G.*, and **Swallow**, *H. T. S.*, alumina catalysts for vapour-phase organic dehydrations, deaminations, etc., 267.
Feigl, *F.*, and **Suter**, *H. A.*, a contribution to the chemistry of the inner complex salts of dimethylglyoxime, 378.
Felton, *D. G. I.* See **King**, *F. E.*
Finar, *I. L.* See **Wilkinson**, *J. H.*
Flemons, *G. F.* See **Baker**, *W.*
Flett, *M. St. C.*, the application of infra-red spectroscopy to structural problems in the anthraquinone field, 1441.
Flood, *A. E.*, **Hirst**, *E. L.*, and **Jones**, *J. K. N.*, quantitative analysis of mixtures of sugars by the method of partition chromatography. Part I. Standardisation of procedure, 1679.
Fodor, *G.*, and **Wein**, *J.*, synthesis of some derivatives of 3 : 4-diphenyl-*n*-hexane, 684.
a new preparation of 3 : 4-bis-(3′- : 4′-dihydroxyphenyl)-*n*-hexane, 890.
Fodor, *G.* See also **Bruckner**, *V.*, and **Földi**, *Z.*
Földi, *Z.*, **Fodor**, *G.*, and **Demjén**, *I.*, investigations relating to the synthesis of patulin, 1295.
Földi, *Z.*, and **Kollonitsch**, *J.*, addition of thiol compounds to the double bond. Part I. Preparation of tertiary mercapto-acids, 1683.
Forrest, *H. S.*, **Fuller**, *A. T.*, and **Walker**, *J.*, chemotherapeutic agents of the sulphone type. Part III. Effect of homologation on the antibacterial activity of *p*-methylsulphonylbenzamidine and *p*-methylsulphonylbenzylamine hydrochlorides, 1501.
Forrest, *H. S.*, and **Walker**, *J.*, chemotherapeutic agents of the sulphone type. Part IV. Part V. 2 : 5-Disubstituted derivatives of pyridine, 1506, 1939.
Forrest, *J.*, and **Tucker**, *S. H.*, the condensation of fluorene with acetone. Part IV. Synthesis of 2 : 4-dimethylfluoranthene, 1137.
Fort, *G.*, and **McLean**, *A.*, derivatives of trishydroxymethylnitromethane, 1902.
condensation of nitromethane with aldehydes; derivatives of 1-nitropent-3-en-2-ol, 1907.
Foster, *R. T.*, and **Robertson**, *Alexander*, furano-compounds. Part VI. A synthesis of karanjic acid, 115.
Foster, *R. T.*, **Robertson**, *Alexander*, and **Bushra**, *A.*, furano-compounds. Part VII. A synthesis of 2 : 3-dihydropsoralene, 2254.
Frankland, *P. F.*, obituary notice of, 1996.
Fuller, *A. T.*, **Harington**, (*Sir*) *C.*, **Pitt-Rivers**, (*Mrs.*) *R.*, and **Stephen**, (*Miss*) *J. M. L.*, some derivatives of *p*-aminobenzoic acid, 241.
Fuller, *A. T.* See also **Elliott**, *D. F.*, and **Forrest**, *H. S.*
Fuller, *H. J.* See **Irving**, *H.*

G.

Galinowski, *S.*, and **Urbański**, *T.*, products of nitration of some derivatives of dimethylaniline, auramine, and crystal-violet, 2169.
Garforth, (*Miss*) *F. M.*, and **Ingold**, *C. K.*, excited states of benzene. Part II. Analysis of the first ultraviolet band system of the absorption spectrum of benzene. Part III. Analysis of the first ultraviolet band system of the fluorescence spectrum of benzene. Part IV. Analysis of the first ultraviolet band system of the absorption spectrum of hexadeuterobenzene. Part V. Analysis of the first ultraviolet band system of the fluorescence spectrum of hexadeuterobenzene. Part X. Analysis of the first ultraviolet band system of the absorption spectrum of monodeuterobenzene, 417, 427, 433, 440, 483.
Garforth, (*Miss*) *F. M.*, **Ingold**, *C. K.*, **and Poole**, *H. G.*, excited states of benzene. Part I. Introductory consideration of some spectral properties of vibrations accompanying electronic transitions of benzene and deuterated benzenes. Part VI. Description and analysis of the first ultraviolet band system of the absorption spectrum of 1 : 3 : 5-trideuterobenzene. Part VIII. Description and analysis of the first ultraviolet band system of the absorption spectrum of 1 : 4-dideuterobenzene. Part IX. Description and analysis of the first ultraviolet band system of the absorption spectrum of 1 : 2 : 4 : 5-tetradeuterobenzene. Part XI. Comparisons between the first ultraviolet absorption and fluorescence band systems of isotopically isomeric benzenes, and further determinations of the vibration frequencies of the upper electronic state. Part XII. The effect of an electronic excitation on the geometry, elastic properties, and zero-point energy of the benzene molecule: and the effect of isotopic substitution on the transition energy, 406, 445, 461, 475, 491, 508.
Gasson, *E. J.*, **McCombie**, *H.*, **Williams**, *A. H.*, and **Woodward**, *F. N.*, new organic sulphur vesicants. Part IV. 1 : 2-Di-(2-chloroethylthio)ethane and its analogues, 44.
Gibson, *G. M.* See **Challenger**, *F.*
Gibson, *G. P.*, the autoxidation of methyl oleate and linoleate, and the decomposition of the oxidation products: a theoretical discussion, 2275.
Gibson, *J.* See **Blayden**, *H. E.*
Gilbert, (*Miss*) *V. E.*, and **Stacey**, *M.*, the constitution of a levan produced from sucrose by *Pseudomonas morsprunorum* (Wormald), 1560.
Gillam, *A. E.*, **Moss**, *D. G.*, and **West**, *T. F.*, observation on the absorption spectra of terpenoid compounds. Part VI. "*iso*Cadinene," 1306.
Gillespie, *D. T. C.*, **Macbeth**, *A. K.*, and **Mills**, *J. A.*, reactions of $\alpha\beta$-unsaturated cyclic aldehydes and ketones. Part VI. (−)-*cis*- and (−)-*trans*-Cryptol from (−)-cryptone, 996.
Gindy, *M.* See **Baddar**, *F. G.*
Given, *P. H.*, and **Hammick**, *D. L.*, some catalysed gas-phase reactions of aromatic hydrocarbons. Part IV. The polymethylbenzenes formed in the reactions of dimethyl ether with benzene, toluene, and the xylenes, 2154.
Glascock, *R.* See **Arrol**, *W. J.*
Glaser, *G.* See **Clarke**, *J. R.*
Glasner, *A.* See **Bobtelsky**, *M.*
Gleed, *S. W.*, and **Peters**, *A. T.*, halogenation of *m*-5- and *m*-2-xylenol; mixed chlorobromo-derivatives, 209.
Goldacre, *R.* See **Albert**, *A.*
Goldberg, *A. A.*, and **Kelly**, *W.*, the addition of hydrogen sulphide to 2-phenyl-Δ^2-oxazoline and benzoylethyleneimine: attempted synthesis of fused thiazolidine–butyroazlactone ring systems, 1919.
Goldsworthy, *L. J.*, **Harding**, *G. F.*, **Norris**, *W. L.*, **Plant**, *S. G. P.*, and **Selton**, *B.*, some sulphides containing the 2-chloroethyl group, 2177.
Goldsworthy, *L. J.*, **Hook**, *W. H.*, **John**, *J. A.*, **Plant**, *S. G. P.*, **Rushton**, *J.*, and **Smith**, *L. M.*, compounds of diarylcyanoarsine type, 2208.
Goldsworthy, *L. J.* See also **Childs**, *A. F.*
Gowenlock, *A. H.*, **Newbold**, *G. T.*, and **Spring**, *F. S.*, synthesis of alloxazine from 2-aminoquinoxaline-3-carboxyamide, 517.
Graham, *W.* See **Curd**, *F. H. S.*
Gregory, (*Miss*) *H.*, **Overend**, *W. G.*, and **Wiggins**, *L. F.*, the conversion of sucrose into pyridazine derivatives. Part V. Experiments on the synthesis of 3-amino-6-methylpyridazine and of its sulphanilamido-derivative, 2199.
Gregory, (*Miss*) *H.* See also **Homer**, *R. F.*
Grove, (*Miss*) *D. H.* See **Armstrong**, *G. P.*
Grove, *J. F.* See **Ashley**, *J. N.*
Gulland, *J. M.*, obituary notice of, 1476.
Gulland, *J. M.*, and **Overend**, *W. G.*, benzylidene guanosine, 1380.
Gulland, *J. M.*, and **Smith**, *H.*, the constitution of yeast ribonucleic acid. Part XII. Synthesis of cytidine-2′-phosphate. Part XIII. The synthesis of diuridine-2′ : 2′-phosphate, 1527, 1532.

H.

Hall, (*Miss*) *D. M.*, the attempted rearrangement of some arylbenziminoquinolyl ethers, 1603.

Hall, (*Miss*) *D. M.*, and **Turner,** *E. E.*, structure and antimalarial activity. Part III. Some benziminazoles, 1909.
Hall, *R. H.*, and **Hey,** *D. H.*, methyl derivatives of 1 : 4 : 5 : 8-tetra-aminoanthraquinone, 736.
Halsall, *T. G.* See **Brown,** *F.*
Hamer, (*Miss*) *F. M.*, **Rathbone,** *R. J.*, and **Winton,** (*Miss*) *B. S.*, some trinuclear cyanine dyes. Part II. Neocyanines with dissimilar nuclei, 1872.
Hamilton, *A.*, **Moggridge,** *R. C. G.*, and **Woodward,** *F. N.*, new organic sulphur vesicants. Part V. 2-Chloroethyl 2-chloro*iso*propyl sulphide, 47.
Hammick, *D. L.*, and **Roberts,** *M.*, some catalysed gas-phase reactions of aromatic hydrocarbons. Part II. The interaction of benzene and ethylene, 73.
Hammick, *D. L.*, and **Thewlis,** *B. H.*, a preparation of lepidine, 1457.
Hammick, *D. L.* See also **Armstrong,** *G. P.*, **Asquith,** *R. S.*, **Brown,** *B. R.*, and **Given,** *P. H.*
Harding, *G. F.*, **Plant,** *S. G. P.*, and **Weeks,** *G. A.*, the preparation of certain urethanes and their conversion into *N*-nitroso-derivatives; some chloronitro-compounds of the type CRR′Cl·CCl(NO$_2$)R″, 2320.
Harding, *G. F.* See also **Childs,** *A. F.*, and **Goldsworthy,** *L. J.*
Harington, (*Sir*) *C.* See **Elliott,** *D. F.*, and **Fuller,** *A. T.*
Harley-Mason, *J.*, melanin and its precursors. Part I. The synthesis of 5 : 6 : 5′ : 6′-tetrahydroxyindigo, 1244.
Harris, *G.* See **Cook,** *A. H.*
Harris, *I.* See **Bircumshaw,** *L. L.*
Harris, *R. J. C.*, and **Thomas,** *J. F.*, the isolation of uridine from yeast ribosenucleic acid, 1936.
Hartley, *E. G. T.*, obituary notice of, 899.
Hartog, *P. J.*, obituary notice of, 901.
Hartwell, *E. J.*, **Richards,** *R. E.*, and **Thompson,** *H. W.*, the vibration frequency of the carbonyl linkage, 1436.
Hassall, *C. H.*, the action of hydrogen peroxide on symmetrical triketones, 50.
Hassall, *C. H.* See also **Briggs,** *L. H.*
Haworth, (*Sir*) *N.*, **Kent,** *P. W.*, and **Stacey,** *M.*, the constitution of a specific somatic polysaccharide from *M. tuberculosis* (human strain), 1211.
the constitution of a lipoid-bound polysaccharide from *M. tuberculosis* (human strain), 1220.
Haworth, (*Sir*) *N.* See also **Bourne,** *E. J.*
Haworth, *R. D.*, **Moore,** *B. P.*, and **Pauson,** *P. L.*, purpurogallin. Part I., 1045.
Haworth, *R. D.*, and **Robinson,** *S.*, synthetic antimalarials. Part XXVII. Some derivatives of phthalazine, quinoxaline, and isoquinoline, 777.
Haseldine, *R. N.* See **Banks,** *A. A.*
Head, *F. S. H.*, formation of tartaric acid by oxidation and hydrolysis of oxycelluloses produced by dinitrogen tetroxide, 1135.
Heap, *R.*, and **Saunders,** *B. C.*, esters containing phosphorus. Part VII. Substituted diaminofluorophosphine oxides, 1313.
Heilbron, (*Sir*) *I.*, recent developments in the vitamin A field, 386.
Heilbron, (*Sir*) *I.* See also **Capp,** *C. W.*, **Chatterjee,** *R.*, and **Cook,** *A. H.*
Hems, *B. A.* See **Elks,** *J.*
Henbest, *H. B.*, and **Jones,** *E. R. H.*, studies in the sterol group. Part XLIX. 7-Substituted cholesterol derivatives and their stereochemistry (Part II). Esters of the epimeric 7-hydroxycholesterols. Part L. 7-Substituted cholesterol derivatives and their stereochemistry (Part III). 7-Alkoxycholesterol derivatives, 1792, 1798.
Henbest, *H. B.* See also **Bide,** *A. E.*
Hendry, *J. A.* See **Birtwell,** *S.*, and **Curd,** *F. H. S.*
Henshall, *T.* See **Ashley,** *J. N.*, and **King,** *F. E.*
Herington, *E. F. G.* See **Coulson,** *E. A.*
Hewett, *C. L.*, isomers of 2-chlorovinyldichloroarsine, 1203.
Hewett, *C. L.*, **Lermit,** *L. J.*, **Openshaw,** *H. T.*, **Todd,** *A. R.*, **Williams,** *A. H.*, and **Woodward,** *F. N.*, derivatives of arsacridine. Part I., 292.
Hey, *D. H.*, and **Morris,** *D. S.*, the synthesis of 2-*cyclo*hexyl-6-methylheptane, 48.
the formation of ketones from semicarbazones by the action of nitrous acid, 2319.
Hey, *D. H.*, and **Walker,** *E. W.*, union of aryl nuclei. Part VII. Reactions with acyl peroxides, 2213.
Hey, *D. H.*, and **Waters,** *W. A.*, the free-radical reactions of the aromatic diazo-compounds, 882.
Hey, *D. H.* See also **Carter,** *P. R.*, **Catch,** *J. R.*, and **Hall,** *R. H.*
Heyworth, *F.* See **Hodgson,** *H. H.*
Hickinbottom, *W. J.*, reactions of unsaturated compounds. Part VII. The mechanism of the formation of unsaturated alcohols from olefins by the action of organic per-acids, 1331.
Hickinbottom, *W. J.* See also **Byers,** *A.*
Hilditch, *T. P.*, structural relationships in the natural unsaturated higher fatty acids, 243.
Hill, *L. M.*, the system ammonia–sulphur dioxide–water at 25°, 76.
Hinshelwood, (*Sir*) *C.*, presidential address, 531.
Hinshelwood, (*Sir*) *C.* See also **Lewis,** *P. R.*, **Peacocke,** *A. R.*, **Rigby,** *H. A.*, and **Stubbs,** *F. J.*
Hirst, *E. L.*, and **Jones,** *J. K. N.*, the structure of egg-plum gum. Part II. The hydrolysis products obtained from the methylated degraded gum, 120.
the galactomannan of carob-seed gum (gum gatto), 1278.
pectic substances. Part VIII. The araban component of sugar-beet pectin, 2311.
Hirst, *E. L.*, **Jones,** *J. K. N.*, and **Roudier,** *A. J.*, structure of acorn starch, 1779.
Hirst, *E. L.* See also **Brown,** *F.*, **Campbell,** *W. G.*, and **Flood,** *A. E.*
Hodgson, *H. H.*, the decomposition reactions of the aromatic diazo-compounds in aqueous solution explained on simple electronic theory, and without recourse to the current free-radical hypothesis, 348.
the structures of Hantzsch's isomeric diazocyanides; a reaffirmation of the structural as opposed to the geometrical viewpoint, with a critical review of the properties of the alleged *cis*-azobenzene, 1097.
Hodgson, *H. H.*, and **Bailey,** *D.*, the isolation of the hitherto unknown *anti*-diazosulphonates in the naphthalene series, with improved preparations of 2- and 4-nitro- and 4-chloro-1-naphthylamine, 1183.
Hodgson, *H. H.*, and **Dixon,** *S.*, the preparation of 4 : 4′-diamino- and 4 : 4′-dihydroxy-2 : 2′-dinaphthyl, 1714.
Hodgson, *H. H.*, and **Dodgson,** *D. P.*, some derivatives of benz-1-thia-2 : 3-diazole, the nature of the thiadiazole ring, and a note on the thiolation of 2-chloro-5-nitroaniline, 870.
the elimination of sulphur in certain reductions of the 2 : 2′ : 4 : 4′-tetranitrodiphenyl mono- and di-sulphides, and an alternative route to the preparation of some 5-substituted benz-1-thia-2 : 3-diazoles, 1002.
improved preparations of 3 : 3′-dinitro- and 3 : 3′-diaminodiphenylamine, together with some derivatives, 1004.
the nitration of benz-1-thia-2 : 3-diazole and the synthesis of 7-nitro-, 5-methyl-, and 7-nitro-5-methyl-benz-1-thia-2 : 3-diazole, with improved preparations of 1-chloro-2 : 6-dinitrobenzene and 2-chloro-3-nitroaniline, 1006.
the preparation of *N*-(2 : 4-dinitrophenyl)- and of *N*-(2 : 6-dinitrophenyl)phthalimide, 1995.
Hodgson, *H. H.*, **Dodgson,** *D. P.*, and **Smith,** *E. W.*, the preparation of 2 : 2′-dichloro-4 : 4′-dinitrodiphenyl sulphide and 2′-chloro-4 : 4′-dinitro-2-aminodiphenyl sulphide, with some derivatives and attempts at cyclisation to thiazines, 1104.
Hodgson, *H. H.*, **Heyworth,** *F.*, and **Ward,** *E. R.*, the replacement of the diazonium by the nitro-group. Part IV. Decompositions involving neutral solutions of diazonium salts, with facile preparations of *o*- and *p*-dinitrobenzene, 1512.
Hodgson, *H. H.*, and **Ward,** *E. R.*, rapid preparation of a solution of sodium hydrogen sulphide, 242.
the decomposition reactions of sodium aryldiazoates. Part I. Replacement of the diazo- by the nitro-group in alkaline solution with sodium nitrite, 556.
reactions of polynitro-aromatic compounds with alkaline sulphides. Part I. Aryl monosulphide formation by interaction of sodium thioaryloxides with polynitro-aromatic compounds containing labile nitro-groups, 2017.
Hoggarth, *E.* See **Curd,** *F. H. S.*
Holland, *A.*, **Lythgoe,** *B.*, and **Todd,** *A. R.*, experiments on the synthesis of purine nucleosides. Part XVIII. A synthesis of 9-D-glucopyranosidoadenine, 965.
Holland, *D. O.*, and **Robinson,** *F. A.*, preparation of water-soluble derivatives of 2-methylnaphthalene, 182.

Holland, *R. A.* See **Chaudhury**, *D. N.*, and **King**, *H. I.*
Hollingsworth, *B. L.*, and **Petrow**, *V.*, new syntheses of heterocyclic compounds. Part IX. Tetrahydrophenanthridines, 1537.
Holt, *S. J.*, and **Petrow**, *V.*, carbazoles, carbolines, and related compounds. Part II. Transformations of some quaternary salts of quindoline. Part III. Quinindoline derivatives, 919, 922.
Homer, *R. F.*, **Gregory**, (*Miss*) *H.*, **Overend**, *W. G.*, and **Wiggins**, *L. F.*, the conversion of sucrose into pyridazine derivatives. Part IV. Further sulphanilamides derived from 6-methyl-3-pyridazone, 2195.
Homer, *R. F.*, **Gregory**, (*Miss*) *H.*, and **Wiggins**, *L. F.*, the conversion of sucrose into pyridazine derivatives. Part III. Constitutional studies on the products of chlorination of 2 : 6-dimethyl-3-pyridazone, 2191.
Hook, *W. H.* See **Goldsworthy**, *L. J.*
Hooper, *D.*, obituary notice of, 253.
Howard, *H. T.* See **Atherton**, *F. R.*
Hu, *P. F.* See **Burton**, *H.*
Huang, *H. T.* See **Cornforth**, *J. W.*
Hughes, *E. D.*, **Ingold**, *C. K.*, and **Mandour**, *A. M. M.*, mechanism of elimination reactions. Part XV. Olefin elimination from *sec.*-*iso*amyl iodide and from the *sec.*-*iso*amyldimethylsulphonium ion, 2090.
Hughes, *E. D.*, **Ingold**, *C. K.*, and **Maw**, *G. A.*, mechanism of elimination reactions. Part XII. Kinetics of olefin eliminations from ethyl, -*n*-propyl-, -*n*-butyl, -*iso*butyl-, and 2-phenylethyl-dimethylsulphonium salts in alkaline alcoholic media, 2072.
Hughes, *E. D.*, **Ingold**, *C. K.*, **Maw**, *G. A.*, and **Woolf**, *L. I.*, mechanism of elimination reactions. Part XIII. Kinetics of olefin elimination from *iso*propyl-, *sec.*-butyl-, and 1-phenylethyl-dimethylsulphonium salts in alkaline alcoholic media, 2077.
Hughes, *E. D.*, **Ingold**, *C. K.*, and **Woolf**, *L. I.*, mechanism of elimination reactions. Part XIV. Kinetics of olefin elimination from *tert.*-butyl- and *tert.*-amyl-dimethylsulphonium salts in alkaline and acidic alcoholic media, 2084.
Hughes, *E. D.* See also **Catchpole**, *A. G.*, **Cooper**, *K. A.*, **De La Mare**, *P. B. D.*, **Dhar**, *M. L.*, and **Dostrovsky**, *I.*
Human, *J. P. E.*, and **Mills**, *J. A.*, the formylation of amines with ethyl formate, 1457.
Hunter, *L.* See **Barker**, (*Mrs.*) *M.*
Hunter, *R. F.*, **Lomer**, *T. R.*, **Vand**, *V.*, and **Williams**, *N. E.*, *X*-ray investigation of some oxidation products of β-carotene, 710.
Hunter, *R. F.* See also **Edisbury**, *J. R.*
Hutchinson, *S. K.* See **Addison**, *C. C.*
Hutchinson, *W. C.* See **Dobson**, *J.*

I.

Iley, *R.*, and **Riley**, *H. L.*, the deposition of carbon on vitreous silica, 1362.
Ing, *H. R.*, the preparation of 2 : 3-dimercaptopropanol from 2 : 3-dichloropropanol, 1393.
Ingles, *O. G.*, and **Israel**, *G. C.*, the oxidation of some aldoses by alkaline solutions of iodine, 810.
Ingold, *C. K.* See **Best**, *A. P.*, **Catchpole**, *A. G.*, **Cooper**, *K. A.*, **De La Mare**, *P. B. D.*, **Dhar**, *M. L.*, **Dostrovsky**, *I.*, **Garforth**, (*Miss*) *F. M.*, and **Hughes**, *E. D.*
Irving, *F.*, and **Johnson**, *A. W.*, a synthesis of 3-acyl- and 3-aroyl-*meso*benzanthrones, 2037.
Irving, *H.*, and **Fuller**, *H. I.*, the action of amines upon esters. Part II., 1989.
Iskander, *Y.*, the anionic nature of the desyl and the α-benzoylbenzhydryl radical as compared with the cationoid reactivity of the triphenylmethyl radical; the hydrolysis of thioesters, 1549.
Israel, *G. C.* See **Ingles**, *O. G.*
Ives, *D. J. G.*, and **Nettleton**, *M. R.*, the problem of molecular asymmetry based on isotopic differentiation of hydrogen; an attempted asymmetric synthesis by the Marckwald method, 1085.
Ives, *D. J. G.*, and **Pittman**, *R. W.*, the photochemistry of selenium. Part I. The photochemical oxidation of hydrogen selenide, 766.

J.

Jadhav, *G. V.* See **Bradley**, *W.*
Jeffery, *G. H.*, and **Vogel**, *A. I.*, physical properties and chemical constitution. Part XVI. Ethylenic compounds. Part XVII. Acetylenic compounds and cyanides. Part XVIII. Three-membered and four-membered carbon rings, 658, 674, 1804.
Jeffrey, *G. A.*, **Koch**, *H. P.*, and **Nyburg**, *S. C.*, molecular configuration and isomorphism in the *meso*-αβ-divinyldibenzyl series, 1118.
John, *J. A.* See **Goldsworthy**, *L. J.*
Johnson, *A. W.* See **Irving**, *F.*
Jones, *E. R. H.* See **Bide**, *A. E.*, **Catch**, *J. R.*, and **Henbest**, *H. B.*
Jones, *J. K. N.* See **Brown**, *F.*, **Campbell**, *W. G.*, **Flood**, *A. E.*, and **Hirst**, *E. L.*

K.

Kelly, *W.* See **Goldberg**, *A. A.*
Kemp, *A. D.*, and **Stephen**, *H.*, the preparation of some *N*-substituted derivatives of *p*-toluenesulphonamide, 110.
Kendall, *J. D.*, and **Major**, *J. R.*, preparation of unsymmetrical carbocyanines, 687.
preparation of symmetrical and unsymmetrical neocyanines: structure of the neocyanines, 690.
Kendall, *J. D.* See also **Duffin**, *G. F.*
Keneford, *J. R.*, **Morley**, *J. S.*, and **Simpson**, *J. C. E.*, cinnolines. Part XIX. The preparation and reactions of some 8-nitro-4-hydroxy- and 4-hydroxy-*Bz*-methyl-cinnolines, 1702.
Keneford, *J. R.*, **Schofield**, *K.*, and **Simpson**, *J. C. E.*, cinnolines. Part XVII. A simple method for the preparation of 4-aminocinnolines, 358.
Keneford, *J. R.*, and **Simpson**, *J. C. E.*, cinnolines. Part XVI. 4-Hydroxy-3-methylcinnolines, 354.
Kenner, *G. W.*, **Lythgoe**, *B.*, and **Todd**, *A. R.*, experiments on the synthesis of purine nucleosides. Part XVII. The preparation of 4-glycofuranosidaminopyrimidines, and a synthesis of 9-L-arabofuranosido-2-methylthioadenine, 957.
Kenny, *T. S.* See **Curd**, *F. H. S.*
Kent, *P. W.* See **Haworth**, (*Sir*) *N.*
Kenyon, *J.*, and **Munro**, *N.*, the isolation and some properties of dehydro-l-ascorbic acid, 158.
Kermack, *W. O.* See **Dobson**, *J.*
Kerrigan, *V.* See **Banks**, *A. A.*
Khorana, *H. G.* See **Beer**, *R. J. S.*
King, *F. E.*, **Acheson**, *R. M.*, and **Spensley**, *P. C.*, benziminazole analogues of paludrine, 1366.
King, *F. E.*, **Acheson**, *R. M.*, and **Yorke-Long**, *A. B.*, the synthesis of 7-amino-alloxazines and -*iso*alloxazines, 1926.
King, *F. E.*, and **Felton**, *D. G. I.*, *cyclo*hexa-1 : 3-dione: a reagent for the characterisation of aldehydes, 1371.
King, *F. E.*, **Henshall**, *T.*, and **Whitehead**, *R. L. St. D.*, synthetical and stereochemical investigations of reduced cyclic bases. Part II. The *cis*- and *trans*-decahydroquinolines, 1373.
King, *F. E.*, **King**, *T. J.*, and **Thompson**, *G. B.*, the condensation of isatin and of 1-methylisatin with barbituric acid, 552.
King, *F. E.* See also **Childs**, *A. F.*
King, *H.*, curare alkaloids. Part VII. Constitution of *dextro*tubocurarine chloride. Part VIII. Examination of commercial curare, *Chondrodendron tomentosum* R and P and *Anomospermum grandifolium* Eichl., 265, 1945.
King, *H.*, and **Wright**, *J.*, 2-amino-1 : 3 : 4-indotriazine; the reaction between isatin and aminoguanidine, 2314.
King, *H. I.*, **Holland**, *R. H.*, **Reed**, *F. P.*, and **Robertson**, *Alexander*, analogues of rotenone and related compounds. Part II. Coumarono-(2′ : 3′ : 3 : 4)-coumarins, 1672.
King, *H. I.* See also **Chaudhury**, *D. N.*
King, *H. J. S.*, researches on ammines. Part X. Triammines of bivalent platinum, 1912.
King, *T. J.* See **Clemo**, *G. R.*, and **King**, *F. E.*
Kipling, *J. J.*, the adsorption of acetic acid and *n*-butylamine from aqueous solutions by activated charcoals, 1483.
the behaviour of charcoal columns in the adsorption and desorption of acetic acid in aqueous solution, 1487.

Kiss, *J.* See **Bruckner,** *V.*
Kletz, *T. A.*, and **Sumner,** *A.*, note on the intensity of the double-bond valence vibration in octenes, 1456.
Kletz, *T. A.* See also **Ashdown,** *A.*
Knott, *E. B.*, β-cycloylpropionitriles. Part III. Reduction to 2-cyclyl-Δ^2-pyrrolines and 2-cyclylpyrrolidines, 186.
Koch, *H. P.*, the coupling reaction of cinnamyl halides; *meso*-αβ-divinyldibenzyl and the phenylvinylmethyl radical, 1111.
absorption spectra of dicinnamyl and some related compounds, 1123.
Koch, *H. P.* See also **Jeffrey,** *G. A.*
Koczka, *I.* See **Bruckner,** *V.*
Koebner, *A.* See **Cymerman,** *J.*
Kollonitsch, *J.* See **Földi,** *Z.*
Kon, *G. A. R.*, 4-styrylbenzylamine and 4-styrylbenzyldimethylamine, 224.
Kon, *G. A. R.* See also **Brown,** *M. B.*, and **Everett,** *J. L.*
Kovács, *J.* See **Bruckner,** *V.*
Kurzer, *F.* See **Dorée,** *C.*

L.

Lal, *A. B.*, and **Petrow,** *V.*, cyanine dyes from 2 : 3-dihydro-β-quinindene, 1895.
Landquist, *J. K.* See **Curd,** *F. H. S.*
Latif, *N.* See **Schönberg,** *A.*
Latter, *R. W.* See **Davey,** *W.*
Leake, (*Miss*) *M. W.* See **Earl,** *J. C.*
Leeds, *W. G.* See **Baker,** *W.*
Lefebure, *V.*, obituary notice of, 394.
Le Fèvre, *R. J. W.*, **Taylor,** *C. R.*, and **Whittem,** *R. N.*, the condensation of benzoin with quinol or resorcinol 1992.
Le Fèvre, *R. J. W.* See also **Calderbank,** *K. E.*, and **Earl,** *J. C.*
Leon, *J. L.* See **Lora-Tamayo,** *M.*
Lermit, *L. J.* See **Hewett,** *C. L.*
Levi, *D. L.* See **Cottrell,** *T. L.*
Levy, *A. L.* See **Chatterjee,** *R.*, and **Cook,** *A. H.*
Levy, *M. B.* See **Balaban,** *I. E.*
Levy, *N.*, **Scaife,** *C. W.*, and **Wilder-Smith,** *A. E.*, addition of dinitrogen tetroxide to olefins. Part IV. The butylenes, 52.
Lewis, *P. R.*, the growth of coliform bacteria in media containing nitrate and nitrite. Part IV. Some biochemical considerations, 845.
Lewis, *P. R.*, and **Hinshelwood,** (*Sir*) *C.*, the growth of coliform bacteria in media containing nitrate and nitrite. Part I. Adaptation to growth with nitrate and nitrite as nitrogen sources. Part II. Influence of ammonia and of aeration, and the coupling of the oxidation–reduction systems involved. Part III. The later stages of reduction of nitrite, 824, 833, 841.
Lister, *B. A.*, and **Smith,** *M. L.*, the fractionation of cerium (III) and neodymium mixtures on an ion-exchange column, 1272.
Llewellyn, *F. J.*, and **Whitmore,** *F. E.*, the crystal structure of *s*-bisnitroaminoethane (ethylene dinitroamine), 1316.
Lloyd, (*Miss*) *D. J.*, obituary notice of, 1727.
Lomer, *T. R.* See **Hunter,** *R. F.*
Lora-Tamayo, *M.*, and **Leon,** *J. L.*, the condensation of 2 : 3-dimethyl-1 : 3-butadiene and *p*-benzoquinone, 1499.
Lord, *K. A.*, decomposition of DDT [1 : 1 : 1-trichloro-2 : 2-di-(4-chlorophenyl)ethane] by basic substances, 1657.
Lythgoe, *B.* See **Davoll,** *J.*, **Holland,** *A.*, and **Kenner,** *G. W.*

M.

Macbeth, *A. K.* See **Gillespie,** *D. T. C.*
McCauley, *H. S.* See **Addison,** *C. C.*
McClelland, *E. W.*, **Rose,** *M. J.*, and **Stammers,** *D. W.*, the formation of thionaphthens from derivatives of phenylthioacetic acid, 81.
McClelland, *E. W.*, and **Stammers,** *D. W.*, some 1 : 3-oxazine derivatives of thionaphthen, 78.
McCombie, *H.* See **Gasson,** *E. J.*
McCoubrey, *A.*, and **Webster,** *W.*, contributions to the chemistry of synthetic antimalarials. Part V. Attempted synthesis of 6-methoxy-8-quinolyl-α-dialkylaminomethylcarbinols. Part VII. The reaction between alloxan and 4-amino-3-(4-diethylamino-1-methylbutylamino)anisole, 97, 1719.
MacDonald, *S. F.*, azlactones and phenylacetic acids derived from the 2-nitro-derivatives of vanillin, *iso*vanillin, and veratraldehyde, 376.
McDowell, *C. A.*, **Emblem,** *H. G.*, and **Moelwyn-Hughes,** *E. A.*, a determination of the structures of the isomeric 2-chlorovinyldichloroarsines, 1206.
Macey, *A.* See **Bourne,** *E. J.*
McGhie, *J. F.* See **Dorée,** *C.*
McGookin, *A.* See **Backhouse,** *T.*
McKail, *J. E.* See **Campbell,** *N.*
Mackle, *H.*, and **Ubbelohde,** *A. R.*, a thermochemical evaluation of the bond strengths in some carbon compounds. Part I. (Methyl carbon)–iodine and (methyl carbon)–magnesium, 1161.
McLean, *A.* See **Fort,** *G.*
McLean, *A. C.* See **Baxter,** *R. A.*
MacNulty, *B. J.* See **Cooper,** *K. A.*
Maddock, *A. G.* See **Emeléus,** *H. J.*
Majer, *J. R.* See **Kendall,** *J. D.*
Malkin, *T.* See **Clarkson,** *C. E.*
Mandour, *A. M. M.* See **Dhar,** *M. L.*, and **Hughes,** *E. D.*
Mangan, *J. L.* See **Briggs,** *L. H.*
Mann, *F. G.* See **Brown,** *Fred.*
Martin, (*Miss*) *E. P.*, and **Pink,** *R. C.*, the solubility of zinc soaps in organic solvents, 1750.
Masterman, *S.* See **Dhar,** *M. L.*
Matchet, *J.* See **Backhouse,** *T.*
Mathieson, *A. McL.* See **Dawson,** *I. M.*
Maw, *G. A.* See **Cooper,** *K. A.*, and **Hughes,** *E. D.*
Maxted, *E. B.*, studies in the detoxication of catalyst poisons. Part VI. Use of a revivable filter-column, 1091.
Maxted, *E. B.*, and **Walker,** *A. G.*, studies in the detoxication of catalyst poisons. Part VII. The self-poisoning effect in the hydrogenation of pyridine. Part VIII. Thionaphthen and the thiophthens, 1093, 1916.
Meade, *E. M.*, and **Woodward,** *F. N.*, some reactions of ethylene sulphide, and a new method of preparation of vicinal dithiols, 1894.
Mears, *M. L.*, the configuration of naturally occurring mixed glycerides. Part IV. The configuration of the major component glycerides of palm oil, 722.
Mellanby, (*Sir*) *E.*, Hopkins Memorial Lecture, 713.
Menary, *J. W.*, **Ubbelohde,** *A. R.*, and **Wright,** *M. J.*, the propagation of reaction chains in the polymerisation of styrene, 2232.
Miles, *G. L.* See **Emeléus,** *H. J.*
Miller, *S. A.* See **Challenger,** *F.*
Mills, *J. A.* See **Gillespie,** *D. T. C.*, and **Human,** *J. P. E.*
Moelwyn-Hughes, *E. A.* See **McDowell,** *C. A.*
Moffatt, *J. S.* See **Cuthbertson,** *W. W.*
Moggridge, *R. C. G.* See **Hamilton,** *A.*
Montgomery, *R.*, and **Wiggins,** *L. F.*, anhydrides of polyhydric alcohols. Part IX. Derivatives of 1 : 4-anhydrosorbitol from 1 : 4-3 : 6-dianhydrosorbitol. Part XII. The reaction between mannitol and hydrochloric acid, 237, 2204.
Montgomery, *R.* See also **Overend,** *W. G.*
Moore, *B. P.* See **Haworth,** *R. D.*
Morley, *J. S.*, and **Simpson,** *J. C. E.*, the chemistry of simple heterocyclic systems. Part I. Reactions of 6- and 7-nitro-4-hydroxyquinazoline and their derivatives, 360. some *Bz*-substituted-3-nitroquinolines, 2024.
Morley, *J. S.*, **Simpson,** *J. C. E.*, and **Stephenson,** *O.*, derivatives of 2 : 4-dinitrophenylacetone, 1717.
Morley, *J. S.* See also **Keneford,** *J. R.*
Morris, *D. S.* See **Carter,** *P. R.*, and **Hey,** *D. H.*
Morrison, *T. J.*, and **Billett,** *F.*, the measurement of gas solubilities, 2033.
Moss, *D. G.* See **Gillam,** *A. E.*
Mostafa, *A.* See **Schönberg,** *A.*
Moualim, *R. J.*, and **Peters,** *A. T.*, anthraquinone series. Part II. Nitro- and amino-2-*tert.*-butyl- and -*n*-butylanthraquinones, and derived blue acid dyes, 1627.
Moubasher, *R.* See **Schönberg,** *A.*
Mousa, *A. A.* See **Tourky,** *A. R.*
Munro, *N.* See **Kenyon,** *J.*

Murray, *A. G.* See **Curd**, *F. N. S.*
Mustafa, *A.* See **Schönberg**, *A.*

N.

Nettleton, *M. R.* See **Ives**, *D. J. G.*
Newbery, *G.*, obituary notice of, 255.
Newbold, *G. T.*, and **Spring**, *F. S.*, the oxidation of 2-hydroxyquinoxaline and its derivatives with hydrogen peroxide, 519.
hydroxamic acids. Part I. Cyclic hydroxamic acids derived from pyridine and quinoline, 1864.
Newbold, *G. T.*, **Spring**, *F. S.*, and **Sweeny**, *W.*, pyrazine derivatives. Part V. A general method for the synthesis of aminopyrazine derivatives, 1855.
Newbold, *G. T.* See also **Baxter**, *R. A.*, and **Gowenlock**, *A. H.*
Newitt, *D. M.*, and **Weale**, *K. E.*, solution and diffusion of gases in polystyrene at high pressures, 1541.
Newth, *F. H.*, and **Wiggins**, *L. F.*, the conversion of sucrose into furan compounds. Part IV. Some aminotetrahydrofuran derivatives, 155.
Nicholls, *G. A.* See **Briggs**, *L. H.*
Nicholson, *J. S.* See **Barltrop**, *J. A.*
Nineham, *A. W.* See **Childs**, *A. F.*
Norris, *W. L.* See **Childs**, *A. F.*, and **Goldsworthy**, *L. J.*
Norrish, *R. G. W.* See **Bevington**, *J. C.*
Nyburg, *S. C.* See **Jeffrey**, *G. A.*

O.

Ogston, *A. G.* See **Cecil**, *R.*
Openshaw, *H. T.*, and **Todd**, *A. R.*, *p*-(2-chloroethylthio)-phenyldichloroarsine, 374.
Openshaw, *H. T.* See also **Davies**, *R. E.*, and **Hewett**, *C. L.*
Oppegaard, *A. G.*, the periodic system of the chemical elements in three dimensions. (The "Five-five System"), 318.
Overend, *W. G.*, **Montgomery**, *R.*, and **Wiggins**, *L. F.*, anhydrides of polyhydric alcohols. Part XI. The action of phosphorus tribromide on 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol; some new chloro-derivatives of 1 : 4-3 : 6-dianhydrosorbitol, 220.
Overend, *W. G.* See also **Gregory**, (*Miss*) *H.*, **Gulland**, *J. M.*, and **Homer**, *R. F.*
Oxley, *P.*, **Partridge**, *M. W.*, and **Short**, *W. F.*, amidines. Part VIII. Preparation of amidines from cyanides, ammonia or an amine, and an ammonium or substituted-ammonium salt, 303.
Oxley, *P.*, **Peak**, *D. A.*, and **Short**, *W. F.*, amidines. Part X. Preparation of amidines from substituted amides, a sulphonyl chloride, and an amine, 1618.
Oxley, *P.*, and **Short**, *W. F.*, amidines. Part IX. Preparation of substituted amidines from ketoxime sulphonates and ammonia or amines, 1514.

P.

Palin, *D. E.*, and **Powell**, *H. M.*, the structure of molecular compounds. Part V. The clathrate compound of quinol and methanol. Part VI. The β-type clathrate compounds of quinol, 571, 815.
Parkes, *G. D.*, substitution in 3 : 4-dialkylphenols, 2143.
Parkes, *G. D.*, and **Farthing**, *A. C.*, derivatives of 2 : 4 : 6-trinitrotoluene: monoreduction of polynitro-compounds, 1275.
Partington, *J. R.*, and **Torto**, *F. G.*, activity coefficients of zinc iodide, 216.
Partington, *J. R.*, and **Whynes**, *A. L.*, the action of nitrosyl chloride on some metals and their compounds, 1952.
Partington, *R. G.*, and **Danby**, *C. J.*, the thermal decomposition of *n*-hexane, 2226.
Partridge, *M. W.* See **Oxley**, *P.*
Pauling, *L.*, the modern theory of valency, 1461.
Pausacker, *K. H.*, and **Robinson**, (*Sir*) *R.*, strychnine and brucine. Part L. Experiments with pseudostrychnine, dihydropseudostrychnine, and *neo*strychnine, 951.
Pauson, *P. L.* See **Haworth**, *R. D.*
Peacocke, *A. R.*, and **Hinshelwood**, (*Sir*) *C.*, the adaptation of bacteria to acridine derivatives; the influence of pH, 1235.
the absorption of antibacterial substances (2 : 8-diaminoacridine and methylene-blue) by cells of *Bact. lactis aerogenes*, 2290.
Peak, *D. A.* See **Oxley**, *P.*
Peat, *S.* See **Bourne**, *E. J.*
Peevers, *R. W.* See **Bide**, *A. E.*
Penney, (*Miss*) *M.* See **Bradfield**, *A. E.*
Penny, *G. F.* See **Attenburrow**, *J.*
Perman, *E. P.*, obituary notice of, 256.
Peters, *A. T.*, **Pringle**, *G. T.*, and **Rowe**, *F. M.*, a reaction of diazosulphonates derived from β-naphthol-1-sulphonic acid. Part XXIV. The phthalazine reaction with bases not containing a nitro-group; derivatives of halogenobenzene-2-naphthol-1-diazosulphonates, 597.
Peters, *A. T.*, **Rowe**, *F. M.*, and **Brodrick**, *C. I.*, a reaction of certain diazosulphonates derived from β-naphthol-1-sulphonic acid. Part XXVI. Phthalazine and *iso*indolinone compounds derived from aniline, 1249.
Peters, *A. T.* See also **Brodrick**, *C. I.*, **Elston**, *C. H. R.*, **Gleed**, *S. W.*, **Moualin**, *R. J.*, and **Rowe**, *F. M.*
Petrow, *V.*, and **Saper**, *J.*, some 5-azaquinoxalines and 4-azabenziminazoles, 1389.
Petrow, *V.* See also **Edwards**, *W. G. H.*, **Hollingsworth**, *B. L.*, **Holt**, *S. J.*, and **Lal**, *A. B.*
Philip, *R.* See **Cook**, *J. W.*
Phillips, *J.* See **Albert**, *A.*
Pianka, *M.*, and **Barany**, *H. C.*, esters of 1-hydroxy-2-naphthoic acid, and naphthol-blue dyes therefrom, 309.
Picard, *C. W.*, **Reid**, *E.*, **Reynolds**, (*Miss*) *J.*, and **Seymour**, *D. E.*, the preparation of N^4-carboxyacylsulphonamides. Part II. The synthesis of N^4-phthalylsulphanilamide derivatives, 821.
Pink, *R. C.* See **Martin**, (*Miss*) *E. P.*
Pinsent, *B. R. W.* See **Everett**, *D. H.*
Pitt-Rivers, (*Mrs.*) *R.* See **Fuller**, *A. T.*
Pittman, *R. W.* See **Ives**, *D. J. G.*
Plant, *S. G. P.* See **Bannister**, *B.*, **Childs**, *A. F.*, **Goldsworthy**, *L. J.*, and **Harding**, *G. F.*
Platt, *B. C.*, 2-hydroxy- and 2-amino-derivatives of 6- and 7-methylquinoxaline, 1310.
Platt, *B. C.*, and **Sharp**, *T. M.*, N^1-sulphanilamides derived from aminoquinoxalines and aminomethylquinoxalines, 2129.
Pollard, *F. H.*, and **Woodward**, *P.*, the growth of titanium nitride on hot filaments, 1709.
Polya, *J. B.*, and **Tardrew**, *P. L.*, amides. Part I. Preparation of diacetimide, 1081.
Poole, *H. G.* See **Garforth**, *F. M.*
Powell, *H. M.*, the structure of molecular compounds. Part IV. Clathrate compounds, 61.
Powell, *H. M.* See also **Palin**, *D. E.*
Pringle, *G. T.* See **Peters**, *A. T.*

R.

Rangwala, *Y. I.* See **Rowe**, *F. M.*
Raphael, *R. A.*, compounds related to penicillic acid. Part III. Synthesis of penicillic acid, 1508.
Rathbone, *R. J.* See **Hamer**, (*Miss*) *F. M.*
Raudnitz, *H.*, dibenzylidene- and di*iso*propylidene-glyoxal, 763.
Record, *B. R.*, ultracentrifugal and diffusion characteristics of methylated glycogen, 1567.
Record, *B. R.*, and **Stacey**, *M.*, some physical properties of the specific polysaccharides from the types I, II, and III pneumococcus, 1561.
Redlich, *O.*, composition, pressure, and temperature relationships in binary azeotropic systems, 1987.
Reed, *F. P.* See **King**, *H. I.*
Reid, *E.* See **Picard**, *C. W.*
Reid, *T. J.*, and **Ubbelohde**, *A. R.*, the effect of metallic impurities in magnesium on the formation of Grignard compounds, 1597.
Reynolds, (*Miss*) *J.* See **Picard**, *C. W.*
Reynolds, *N. G.* See **Barker**, (*Mrs.*) *M.*

Richards, *J. H.*, **Robertson,** *Alexander*, and **Ward,** *J.*, experiments on the synthesis of rotenone and its derivatives. Part XV., 1610.
Richards, *R. E.*, the thermodynamic functions of the vinyl halides, 1931.
Richards, *R. E.* See also **Hartwell,** *E. J.*
Richardson, (*Miss*) *D. N.* See **Crowther,** *A. F.*
Rigby, *H. A.*, **Danby,** *C. J.*, and **Hinshelwood,** (*Sir*) *C.*, the spontaneous low-temperature polymerisation of acetaldehyde, 234.
Riley, *D. W.* See **Barrer,** *R. M.*
Riley, *H. L.* See **Blayden,** *H. E.*, and **Iley,** *R.*
Roberts, *M.* See **Hammick,** *D. L.*
Robertson, *Alan*, and **Waters,** *W. A.*, studies of the autoxidation of tetralin. Part I. Investigation of autoxidation products. Part II. The decomposition of tetralin hydroperoxide. Part III. An interpretation of the kinetics of autoxidation, 1574, 1578, 1585.
Robertson, *Alexander.* See **Backhouse,** *T.*, **Beer,** *R. J. S.*, **Boyd,** *J.*, **Bridge,** *W.*, **Chaudhury,** *D. N.*, **Clarke,** *J. R.*, **Dean,** *F. M.*, **Foster,** *R. T.*, **King,** *H. I.*, and **Richards,** *J. H.*
Robertson, *J. M.* See **Dawson,** *I. M.*
Robertson, *P. W.* See **De La Mare,** *P. B. D.*, and **Rothbaum,** *H. P.*
Robinson, *F. A.* See **Holland,** *D. O.*
Robinson, (*Sir*) *R.* See **Bailey,** *A. S.*, and **Pausacker,** *K. H.*
Robinson, *R. A.*, the adsorption of water vapour on insulin and plasma albumin, 1083.
Robinson, *R. A.*, and **Selkirk,** *R. C.*, the system hydrogen chloride–dioxan–water at 25°, 1460.
Robinson, *S.* See **Haworth,** *R. D.*
Rose, *F. L.* See **Ashworth,** *R. de B.*, **Birtwell,** *S.*, **Cliffe,** *W. H.*, **Crowther,** *A. F.*, and **Curd,** *F. H. S.*
Rose, *J. D.* See **Charlish,** (*Mrs.*) *J. L.*
Rose, *M. J.* See **McClelland,** *E. W.*
Ross, *W. C. J.*, lipoid-soluble alloxazine derivatives, 219.
some derivatives of 4-styrylpyrimidine, 1128.
Ross, *W. C. J.* See also **Brown,** *D. M.*
Rothbaum, *H. P.*, **Ting,** *I.*, and **Robertson,** *P. W.*, the kinetics of halogen addition to unsaturated compounds. Part XIII. αβ-Unsaturated ketones and quinones, 980.
Roudier, *A. J.* See **Hirst,** *E. L.*
Rowe, *F. M.*, obituary notice of, 2323.
Rowe, *F. M.*, **Desai,** *R. L.*, and **Peters,** *A. T.*, a reaction of certain diazosulphonates derived from β-naphthol-1-sulphonic acid. Part XXIII. Phthalazine derivatives from 4′-nitro-2′ : 5′-dimethoxybenzene-2-naphthol-1-diazosulphonate, 281.
Rowe, *F. M.*, **Peters,** *A. T.*, and **Rangwala,** *Y. I.*, a reaction of certain diazosulphonates derived from β-naphthol-1-sulphonic acid. Part XXII. Derivatives of 2′-chloro-5′-nitrobenzene-2-naphthol-1-diazosulphonate, 206.
Rowe, *F. M.* See also **Brodrick,** *C. I.*, **Elston,** *C. H. R.*, and **Peters,** *A. T.*
Royer, *R.* See **Buu-Hoi,** *N. P.*
Rushton, *J.* See **Goldsworthy,** *L. J.*
Russell, *W. E.* See **Briggs,** *L. H.*
Rydon, *H. N.*, the synthesis of the nuclear-*C*-methylated tryptophans; a note on the aldehyde reactions for tryptophan, 705.
Ryman, (*Miss*) *B. E.* See **Elks,** *J.*

S.

Said, (*Mrs.*) *A.* See under **Mostafa,** *A.*
Saper, *J.* See **Petrow,** *V.*
Saunders, *B. C.*, and **Stacey,** *G. J.*, esters containing phosphorus. Part IV. Di*iso*propyl fluorophosphonate, 695.
toxic fluorine compounds containing the C–F link. Part I. Methyl fluoroacetate and related compounds, 1773.
Saunders, *B. C.*, **Stacey,** *G. J.*, **Wild,** *F.*, and **Wilding,** *I. G. E.*, esters containing phosphorus. Part V. Esters of substituted phosphonic and phosphonous acids, 699.
Saunders, *B. C.* See also **Chapman,** *N. B.*, and **Heap,** *R.*
Saunders, *L.*, measurement of specific surfaces of calcined and hydrated alumina powders by adsorption of *n*-heptoic acid from aqueous solutions, 969.
Scaife, *C. W.* See **Levy,** *N.*
Schmeidler, *G. A.* See **Barton,** *D. H. R.*
Schönberg, *A.*, stereochemistry of the disalicylides, 891.
Schönberg, *A.*, **Moubasher,** *R.*, and **Mostafa,** *A.*, degradation of α-amino-acids to aldehydes and ketones by interaction with carbonyl compounds, 176.
Schönberg, *A.*, and **Mustafa,** *A.*, the interaction of tetraarylglycols and pyridinium salts, 385.
experiments with diazomethane and its derivatives. Part XIV. Action of diazomethane on (*a*) *N*-acyl compounds and (*b*) *o*-hydroxydiaryl sulphones and the corresponding *peri*-compounds, 605.
Schönberg, *A.*, **Mustafa,** *A.*, **Barakat,** *M. Z.*, **Latif,** *N.*, **Moubasher,** *R.*, and **Mostafa,** *A.*, photochemical reactions, Part XIII. (*a*) Photochemical reactions of ethylenes with phenanthraquinone and with 1 : 2 : 3-triketones. (*b*) Dimerisation reactions in sunlight, 2126.
Schoental, (*Miss*) *R.* See **Cook,** *J. W.*
Schofield, *K.*, and **Simpson,** *J. C. E.*, cinnolines. Part XVIII. The preparation of 3-halogeno-4-hydroxycinnolines, and halogen exchange reactions of diazotised ω-halogeno-*o*-aminoacetophenones, 1170.
Schofield, *K.*, and **Swain,** *T.*, the preparation of *o*-nitroacetophenone, 384.
Schofield, *K.* See also **Keneford,** *J. R.*
Scott, *A. D.* See **Edisbury,** *J. R.*
Scott, (*Miss*) *M.* See **Cliffe,** *W. H.*
Seetharamiah, *A.*, experiments on the synthesis of karanjin, 894.
Selkirk, *R. C.* See **Robinson,** *R. A.*
Selton, *B.* See **Childs,** *A. F.*, and **Goldsworthy,** *L. J.*
Sexton, *W. A.*, and **Spinks,** *A.*, the hydroxymethyl derivative of 2-mercaptobenzthiazole, 1717.
Seymour, *O. E.* See **Picard,** *C. W.*
Sharp, *T. M.* See **Platt,** *B. C.*
Sharp, *W.*, and **Spring,** *F. S.*, pyrazine derivatives. Part VII. The preparation of hydroxypyrazine derivatives by Gastaldi's method, 1862.
Sharpe, *A. G.*, and **Emeléus,** *H. J.*, chemistry of the interhalogen compounds. Part I. The reaction of bromine trifluoride with metallic halides, 2135.
Sharpe, *A. G.* See also **Emeléus,** *H. J.*
Shaw, *G.* See **Cook,** *A. H.*
Shelton, *J. P.* See **Bevan,** *D. J. M.*
Shoppee, *C. W.*, steroids and the Walden inversion. Part III. (*a*) Derivatives of 6-ketocholestane; (*b*) a direct proof of the stereochemical orientation of the hydroxyl group in cholesterol. Part IV. Derivatives of 6-ketositostane and 6 : 17-diketoandrostane, 1032, 1043.
Short, *W. F.* See **Cymerman,** *J.* and **Oxley,** *P.*
Simpson, *J. C. E.*, and **Wright,** *P. H.*, derivatives of 4-chloro- and 6-nitro-quinoline, 1707.
the nitration of 4-aminoquinoline, 2023.
Simpson, *J. C. E.* See also **Keneford,** *J. R.*, **Morley,** *J. S.*, and **Schofield,** *K.*
Simpson, (*Miss*) *M. I.* See **Challenger,** *F.*
Skellon, *J. H.*, the mechanism of oxidation of monoethenoid fatty acids and esters; the course of thermal catalytic oxidation of methyl oleate, 343.
Slack, *R.*, and **Waters,** *W. A.*, a study of the mechanism of oxidation with chromic acid. Part II., 1666.
Slater, *S. N.* See **Campbell,** *A. D.*
Smith, *E. W.* See **Hodgson,** *H. H.*
Smith, *F.*, preparation of mannose, 1989.
Smith, *F.*, and **Webb,** *M.*, the reaction of keto-cholanic acids with bromoacetic ester and cyanoacetic ester, 1358.
Smith, *F.* See also **Cunneen,** *J. I.*
Smith, *H.* See **Gulland,** *J. M.*
Smith, *L. M.* See **Goldsworthy,** *L. J.*
Smith, *M. L.* See **Lister,** *B. A.*
Somerville, *A. R.* See **Cook,** *J. W.*
Spensley, *P. C.* See **King,** *F. E.*
Spinks, *A.* See **Sexton,** *W. A.*
Spring, *F. S.* See **Baxter,** *R. A.*, **Davies,** *R. E.*, **Gowenlock,** *A. H.*, **Newbold,** *G. T.*, and **Sharp,** *W.*
Stacey, *G. J.* See **Saunders,** *B. C.*
Stacey, *M.*, and **Swift,** *G.*, structure of the dextran synthesised from sucrose by a new strain of *Betacoccus arabinosaceous*, 1555.
Stacey, *M.* See also **Gilbert,** (*Miss*) *V. E.*, **Haworth,** (*Sir*) *N.*, and **Record,** *B. R.*
Stammers, *D. W.* See **McClelland,** *E. W.*

Stanley, *R. H.* See **Davies**, *R. E.*
Stephen, *H.* See **Kemp**, *A. D.*
Stephen, (*Miss*) *J. M. L.* See **Fuller**, *A. T.*
Stephenson, *O.* See **Morley**, *J. S.*
Stern, *E. S.* See **Braude**, *E. A.*, and **Cook**, *A. H.*
Steward, *A. W.*, obituary notice of, 396.
Stubbs, *F. J.*, **Williams**, *C. D.*, and **Hinshelwood**, (*Sir*) *C.*, the kinetics of aromatic sulphonation reactions; sulphonation by sulphuric acid in nitrobenzene solution, 1065.
Sumner, *A.* See **Kletz**, *T. A.*
Suter, *H. A.* See **Feigl**, *F.*
Sutherland, *G. B. B. M.* See **Brownlie**, *I. A.*
Sutton, *L. E.* See **Coates**, *G. E.*
Swain, *G.*, a synthesis of DL-dethiobiotin and some related compounds, 1552.
Swain, *T.* See **Schofield**, *K.*
Swallow, *H. T. S.* See **Feachem**, *G.*
Swan, *G. A.*, the fission of non-enolisable ketones by potassium *tert.*-butoxide, 1408.
Swan, *G. A.* See also **Clemo**, *G. R.*
Sweeny, *W.* See **Newbold**, *G. T.*
Swift, *G.* See **Stacey**, *M.*

T.

Tantram, *A. D. S.* See **Bell**, *R. P.*
Tardrew, *P. L.* See **Polya**, *J. B.*
Taylor, *C. R.* See **Le Fèvre**, *R. J. W.*
Taylor, *H. F. W.*, the dissociation constants of benziminazole and certain purine derivatives, 765.
Taylor, *W. I.* See **Briggs**, *L. H.*
Temple, *R. B.* See **Thompson**, *H. W.*
Thewlis, *B. H.* See **Hammick**, *D. L.*
Thomas, (*Miss*) *H.* See **Williams**, *G.*
Thomas, *J. F.* See **Harris**, *R. J. C.*
Thomas, *L. H.*, viscosity and molecular association. Part I. Part II. A relationship between viscosity and vapour pressure of associated liquids, 1345, 1349.
Thompson, *G. B.* See **King**, *F. E.*
Thompson, *H. W.*, the correlation of vibrational absorption spectra with molecular structure, 328.
Thompson, *H. W.*, and **Temple**, *R. B.*, the vibrational spectra and thermodynamic properties of chlorofluoromethanes, 1422.
infra-red spectra of fluorinated hydrocarbons. Part II. "Methyl fluoroform" (1 : 1 : 1-trifluoroethane). Part III., 1428, 1432.
Thompson, *H. W.*, and **Whiffen**, *D. H.*, the infra-red examination of some terpenoid substances, 1412.
Thompson, *H. W.* See also **Armstrong**, *G. P.*, **Drayton**, *G. L.*, **Hartwell**, *E. J.*, and **Whiffen**, *D. H.*
Thorp, *R. H.*, and **Walton**, *E.*, search for new analgesics. Part II. Further homologues of pethidine and the pharmacology of these and other compounds, 559.
Ting, *I.* See **Rothbaum**, *H. P.*
Tittensor, *E.* See **Backhouse**, *T.*
Todd, *A. R.* See **Atherton**, *F. R.*, **Bick**, *I. R. C.*, **Brownlie**, *I. A.*, **Davies**, *R. E.*, **Davoll**, *J.*, **Hewett**, *C. L.*, **Holland**, *A.*, **Kenner**, *G. W.*, and **Openshaw**, *H. T.*
Tompsett, *A. L. L.* See **Childs**, *A. F.*
Torto, *F. G.* See **Partington**, *J. R.*
Tourky, *A. R.*, and **El Wakkad**, *S. E. S.*, studies on some metal electrodes. Part I. Oxide-film formation on copper, and the evaluation of the standard electrode potential of the metal. Part II. The behaviour of the copper electrode in dilute copper sulphate solutions, 740, 749.
Tourky, *A. R.*, and **Mousa**, *A. A.*, studies on some metal electrodes. Part III. Does the antimony electrode behave simply as a metal–metal oxide electrode in air? Part IV. The behaviour of the antimony electrode out of contact with air. Part V. The amphoteric properties of antimony tri- and pent-oxide, 752, 756, 759.
Tucker, *S. H.* See **Forrest**, *J.*
Tully, *K. J.* See **Cottrell**, *T. L.*
Turner, *E. E.* See **Hall**, (*Miss*) *D. M.*

U.

Ubbelohde, *A. E.* See **Mackle**, *H.*, **Menary**, *J. W.*, and **Reid**, *T. J.*
Ultée, *A. J.*, the action of hydrogen chloride on isoprene, 530.
Urbański, *T.* See **Galinowski**, *S.*

V.

Vand, *V.* See **Hunter**, *R. F.*
Vogel, *A. I.*, physical properties and chemical constitution. Part X. *n*-Alkylbenzenes. Part XI. Ketones. Part XII. Ethers and acetals. Part XIII. Aliphatic carboxylic esters. Part XIV. The parachors and the refractivities of the halogens. Part XV. The phenyl group. Part XIX. Five- and six-membered carbon rings. Part XX. Aliphatic alcohols and acids. Part XXI. Aliphatic thiols, sulphides, and disulphides. Part XXII. Some primary, secondary, and tertiary amines. Part XXIII. Miscellaneous compounds; investigation of the so-called co-ordinate or dative link in esters of oxy-acids and in nitroparaffins by molecular refractivity determinations; atomic, structural, and group parachors and refractivities, 607, 610, 616, 624, 644, 654, 1809, 1814, 1820, 1825, 1833.
Vogel, *A. I.* See also **Jeffery**, *G. H.*

W.

Waley, *S. G.*, polyquinolyls, 2008.
Walker, *A. G.* See **Maxted**, *E. B.*
Walker, *E. W.* See **Hey**, *D. H.*
Walker, *J.* See **Forrest**, *H. S.*
Walker, *T.* See **Badger**, *G. M.*
Walls, *L. P.* See **Caldwell**, *A. G.*
Walsh, *A. D.*, bond energies in peroxides, and the energy evolved in the reaction $H + O_2 = HO_2$, 331.
factors influencing the strengths of bonds, 398.
Walton, *E.* See **Thorp**, *R. H.*
Ward, *E. R.* See **Hodgson**, *H. H.*
Ward, *J.* See **Richards**, *J. H.*
Waring, *D. H.* See **Bell**, *F.*
Wassermann, *A.*, alginic acid acetate, 197.
the structure of diketen: potentiometric and conductivity measurements, 1323.
Waters, *W. A.*, the significance of the transition state in aromatic substitution, 727.
Waters, *W. A.* See also **Hey**, *D. H.*, **Robertson**, *Alan*, and **Slack**, *R.*
Weale, *K. E.* See **Newitt**, *D. M.*
Webb, *M.* See **Smith**, *F.*
Weber, *K.*, and **Alperger**, *S.*, the kinetics of photochemical oxidation with dichromate; the oxidation of glycerol, 2119.
Webster, *W.* See **McCoubrey**, *A.*
Weeks, *G. A.* See **Childs**, *A. F.*, and **Harding**, *G. F.*
Weil-Malherbe, *H.*, and **Weiss**, *J.*, colour reactions and adsorption of some aluminosilicates, 2164.
Wein, *J.* See **Fodor**, *G.*
Weiss, *J.* See **Weil-Malherbe**, *H.*
West, *T. F.* See **Gillam**, *A. E.*
Whalley, *W. B.*, a new synthesis of *NN'*-diarylformamidines, 1014.
Whiffen, *D. H.*, and **Thompson**, *H. W.*, infra-red analysis of stereoisomers of "benzene hexachloride" (hexachloro-*cyclo*hexane), 1420.
Whiffen, *D. H.* See also **Thompson**, *H. W.*
White, *J. G.*, the crystal structure of 1 : 12-benzperylene: a quantitative *X*-ray investigation, 1398.
Whitehead, *R. L. St. D.* See **King**, *F. E.*
Whiting, *G. H.*, some physicochemical properties of *cis*-2-chlorovinyldichloroarsine, 1209.
Whitmore, *F. C.*, obituary notice of, 1090.
Whitmore, *F. E.* See **Llewellyn**, *F. J.*
Whittem, *R. N.* See **Le Fèvre**, *R. J. W.*
Whynes, *A. L.* See **Partington**, *J. R.*
Wiggins, *L. F.* See **Bashford**, *V. G.*, **Bourne**, *E. J.*, **Gregory**, (*Miss*) *H.*, **Homer**, *R. F.*, **Montgomery**, *R.* **Newth**, *F. H.*, and **Overend**, *W. G.*
Wild, *F.* See **Saunders**, *B. C.*
Wilder-Smith, *A. E.* See **Levy**, *N.*
Wilding, *I. G. E.* See **Saunders**, *B. C.*

Wilkinson, *J. H.*, and **Finar,** *I. L.*, a study of the properties of fluorine-substituted 5-aminoacridines and related compounds. Part II. 5-Amino-2- and -4-trifluoromethylacridines. Part III. Some 5-amino-1 : 2 : 2′ : 3′-pyridoacridines, 32, 288.
Wilkinson, *P. A.* See **Bide,** *A. E.*
Williams, *A. H.*, and **Woodward,** *F. N.*, new organic sulphur vesicants. Part II. Analogues of 2 : 2′-dichlorodiethyl sulphide and 2 : 2′-di-(2-chloroethylthio)diethyl ether, 38.
Williams, *A. H.* See also **Gasson,** *E. J.*, and **Hewett,** *C. L.*
Williams, *C. D.* See **Stubbs,** *F. J.*
Williams, *G.*, and **Thomas,** (*Miss*) *H.*, short-chain polymerisation of styrene in presence of stannic chloride and hydrogen chloride, 1867.
Williams, *N. E.* See **Hunter,** *R. F.*
Williams, *P. L.* See **Asquith,** *R. S.*
Wilson, *C. L.* See **Best,** *A. P.*
Wilson, *W.*, some 2 : 4-diamino-5-acylamido-6-hydroxypyrimidines, 1157.
tetrahydrofurans related to amidone, 1993.
Wilson, *W.* See also **Catch,** *J. R.*
Winton, (*Miss*) *B. S.* See **Hamer,** (*Miss*) *F. M.*
Wolfenden, *J. H.* See **Cottrell,** *T. L.*
Wood, *J. F.* See **Emeléus,** *H. J.*
Woodcock, *D.* See **Batt,** *R. F.*
Woodward, *F. N.*, new organic sulphur vesicants. Part I. 2 : 2′-Di-(2-chloroethylthio)diethyl ether, 35.
monothioethylene glycol and thiodiglycol, 1892.
Woodward, *F. N.* See also **Gasson,** *E. J.*, **Hamilton,** *A.*, **Hewett,** *C. L.*, **Meade,** *E. M.*, and **Williams,** *A. H.*
Woodward, *P.* See **Pollard,** *F. H.*
Woolf, *L. I.* See **Dhar,** *M. L.*, and **Hughes,** *E. D.*
Wragg, *W. R.* See **Barber,** *H. J.*
Wright, *J.* See **King,** *H.*
Wright, *M. J.* See **Menary,** *J. W.*
Wright, *P. H.* See **Simpson,** *J. C. E.*
Wright, *S. E.*, the constitution of evodione, 2005.

Y.

Yorke-Long, *A. B.* See **King,** *F. E.*

INDEX OF SUBJECTS, 1948.

A.

Abietic acid, oxidation of, tricarboxylic acid and its derivatives from, 1201.
Acenaphthene, synthesis of *as*-hydrocarbons from, 1395.
Acenaphthenesulphonic acid, 3-amino-, acetyl derivative, *S*-benzylisothiuronium salt, 1714.
Acenaphthenone, *p*-bromo-, 2-chloro-5-nitro- and *o*- and *p*-nitro-phenylhydrazones, 1248, 1249.
1-(5-Acenaphthenyliminomethyl)*cyclo*hexan-2-one, 1540.
Acenaphthylene, dimerisation of, 1990.
Acenaphthyleno(7′:8′-2:3)indole, and its derivatives, 1247.
Acenaphthyleno(7′:8′-2:3)indole, 5-bromo-, and 7-chloro-4-nitro-, 1249.
6(or 4)-nitro-, 1-acetyl, -benzoyl, and -cinnamoyl derivatives, 1248.
Acenaphthyleno(7′:8′:2:3)indole-1-carboxylic acid, and 6(or 4)-nitro-, ethyl and methyl esters, 1248.
Acetals, parachors and refractivities of, 616.
Acetaldehyde, polymerisation of, low-temperature, 234.
Acetamidinium picrate, *tri*chloro-, 305.
Acetanilide, *p*-chloro-*o*-nitro-*ω*-chloro-, 1910.
*di*nitro-derivatives, preparation of, 2132.
2-β-Acetanilidovinylbenzoxazole methiodide, 1897.
2-β-Acetanilidovinylbenzthiazole methiodide, 1897.
Acetic acid, adsorption of, from aqueous solutions, by charcoal, 1483, 1487.
allyl ester, addition of chlorine to, 1394.
geranyl ester, spectrum of, infra-red absorption, 1414.
nitro-*tert.*-butyl ester, 57.
Acetic acid, aminocyano-, ethyl ester, thiocyanate, 1344.
bromo-, and chloro-, ethyl esters, reaction of, with ketocholanic acids, 1358.
chloro- and iodo-, 3-chloroallyl esters, 2182.
*di*chloro-, preparation and properties of, and its esters, 1845.
*tri*chloro-, esters, 1845.
fluoro-, alkyl and aryl esters, 1773, 1776.
thiol-, 2:4-diacetamidophenyl ester, 1004.
thiolchloro-, 2-bromo- and 2-chloro-ethyl esters, 1894.
Acetic anhydride, fluoro-, 1778.
Acetoacetic acid, α-amino-, benzoyl derivative, ethyl ester, and its semicarbazone, 315.
1:3-*di*fluoro-, ethyl ester, 1777.
Acetoin. See Acetylmethylcarbinol.
3-Acetomercuri-4-methylpyridine, 200.
Acetone, bromination of, 272.
condensation of, with fluorene, 1137.
β-diethylaminoethyloxime, 185.
halogenation of, in chlorobenzene, 370.
Acetone, amino-, benzoyl derivative, and its 2:4-dinitrophenylhydrazone, 315.
α-bromopropionyl derivatives, 1857, 1858.
Acetonitrile, amino-, reaction of, with carbon disulphide, 201.
thiocyanate, 1344.
Acetophenone, and bromo-, oxime benzene- and *p*-toluenesulphonates, 1518.
Acetophenone, 5:*ω*-*di*bromo-2-amino- and -2-nitro-, and 5-chloro-*ω*-bromo-2-amino- and -2-nitro-, and their pyridinium derivatives, 1173.
ω-halogeno-*o*-amino-, diazotised, halogen exchange with, 1170.
2:5-*di*hydroxy-, 5-benzoyl derivative, 2141.
2:6-*di*hydroxy-, 2:6-dianisyl derivative, 2143.
2:3:6-*tri*hydroxy-, 2:3-di- and 2:3:6-tri-benzyl derivatives, 2141.
o-nitro-, preparation of, 384.
3-Aceto-*m*-toluidide, 4-chloro-5-nitro-, 1009.
Acetoxime benzenesulphonate, 1518.
Acetyl chloride, fluoro-, 1777.
fluoride, fluoro-, 1778.
5-Acetylbenzfuran, 4:5-*di*hydroxy-, 895.
***N*-Acetyldi-(2-chloroethyl)amine**, and *N*-chloro-, 2174.
***p*-Acetyl-αβ-diethylstilbene**, 1080.
3-Acetyldiphenylarsonous acid, 2209.
3-Acetyldiphenylchloroarsine, and 3-chloro-, 2210.
3-Acetyldiphenylcyanoarsine, 2211.
Acetyldithiocarbamic acid, 3-chloroallyl ester, 2182.
Acetylene, conversion of carbon dioxide into, 1534.
Acetylenedicarboxylic acid, esters, 679.
Acetylenic compounds, parachors and refractivities of, 674.
1- or 3-Acetylglyoxaline, 4(5)-amino-2-mercapto-, 4(5)-benzoyl derivative, 1265.
2′-Acetyl guanosine, 1381.
5-Acetylhexoic acid, and its derivatives, 233.
Acetylmethylcarbinyl benzoate, and its semicarbazone, 275.
4-Acetyl-3-methylphenol, 6-amino-, and nitro-, and its methyl ether, 2146.
2-Acetyl-4-methylphenoxyacetic acid, 5-hydroxy-, 5-benzyl derivative, and its ethyl ester, 2259.
2-Acetyl-5-methylphenoxyacetic acid, and its ethyl ester, 2260.
5-Acetylnona-2:7-diene-5-carboxylic acid, 1:9-*di*cyano-, ethyl ester, 234.
5-Acetylnonane-5-carboxylic acid, 1:9-*di*cyano-, ethyl ester, 234.
2-Acetylphenoxyacetic acid, 5-hydroxy-, 5-benzyl derivative, and its ethyl ester, 2258.
***N*-Acetylphenylcarbamyl-3-acetoxythiophen**, 85.
3-Acetyl-3-phenylpentanecarboxylic acid, 1744.
3-Acetyl-4-phenylthiazoline, 5-amino-2-imino-, 5-acetyl-2-benzoyl derivative, 1266.
3-Acetyl-3-phenylundecanecarboxylic acid, 1744.
6-Acetylquinoline, 2010.
***O*-Acetylsalicylic acid**, *O*-fluoro-, 1779.
α-Acetylsuberic acid, α-chloro-, ethyl ester, 1553.
2-(Acetylsulphanilamido)ethyl bromide, 1925.
2-(Acetylsulphanilamido)ethylthiol, 1925.
Acetylsulphanilylethyleneimide, 1925.
3-Acetylthiazoline, 5-amino-2-imino-, 5-acetyl-2-benzoyl derivative, 1265.
3-Acetylthiazoline-4-carboxylic acid, 5-amino-2-imino-, 5-acetyl-2-benzoyl derivative, ethyl ester, 1343.
2-Acetylthio-2-acetyliminazole, 4-amino-, 4-benzoyl derivative, 1265.
2-Acetylthioiminazole, 5-amino-, 5-benzoyl derivative, 1266.
Acids, aliphatic, physical properties and constitution of, 1814.
*mono*carboxylic, branched-chain, preparation of, 1741.
fatty, ethenoid, and their esters, oxidation of, 343.
higher, unsaturated, structure of, 243.
relative strengths of, 1029.
organic, heats of ionisation of, 1016, 1019.
Acidity functions, 1971, 1976.
Acorn starch, structure of, 1779.
Acridine, derivatives, adaptation of bacteria to, 1235.
Acridine, 5-amino-, derivatives, reaction of, with hydrogen sulphide, 1181.
2:8-*di*amino-. See Proflavine.
Acridines, synthesis and reactions of, 1225.
Acridines, amino-, synthesis of, from formic acid and diarylamines, 1225.
5-amino-, fluorine-substituted, properties of, 32, 288.
***N*-Acridyl(5)-*p*-aminobenzoic acid**, 241.
***N*-Acyl compounds**, action of diazomethane on, 605.
Acyl peroxides, reactions of, 2213.
5-Acylamido-6-hydroxypyrimidines, 2:4-*di*amino-, 1157.
Address, presidential, 531.
Adenine, dissociation constants of, 765.
Adenosine, synthesis of, 967.
Adsorbents, mineral, 127, 133.
Adsorption from aqueous solutions by charcoal, 1483, 1487.
of gases on minerals, 135.
Agathis australis, kaurene from, 1888.
Alanine, derivatives of, bacteriostatic action of, 85.

DL-Alanine, preparation of, 1861.
Albumin, plasma, adsorption of water vapour on, 1083.
Alcohols, aliphatic, physical properties and constitution of, 1814.
molecular association of, 1345, 1349.
polyhydric, anhydrides of, 237, 299, 2201, 2204.
spectra of, infra-red absorption, in mixtures with aldehydes, 1454.
unsaturated, formation of, from olefins by action of organic per-acids, 1331.
Aldehydes, condensation of, with nitromethane, 1907.
detection of, with *cyclo*hexa-1:3-dione, 1371.
formation of, from α-amino-acids, 176.
spectra of, infra-red absorption, in mixtures with alcohols, 1454.
αβ-unsaturated cyclic, reactions of, 996.
Aldobionic acid from almond-tree gum, 1677.
Aldohexoses, methylated, periodate oxidation of, with formaldehyde liberation, 993.
Aldoses, oxidation of, by iodine solutions, 810.
Alginic acid acetate, 197.
Alkali sulphides, reactions of, with polynitro-aromatic compounds, 2017.
Alkaloids, curare, 265, 1945.
Daphnandra, 2170.
Senecio, 1891.
Sophora, 1889.
Alkyl *iso*thiocyanates, reaction of, with α-aminonitriles, 2028.
n-Alkyl bromides, kinetics of olefin formation from, 2055, 2058.
tert.-Alkyl bromides, kinetics of olefin formation from, 2065.
n-Alkylbenzenes, parachors and refractivities of, 607.
Alkyl ketones, parachors and refractivities of, 610.
p-Alkylsulphonylbenzylammonium chlorides, preparation of, 381.
Alloxan, reaction of, with 4-amino-3-(4-diethylamino-1-methylbutylamino)anisole, 1719.
Alloxazine, lipoid-soluble derivatives of, 219.
synthesis of, from 2-aminoquinoxaline-3-carboxyamide, 517.
n- and *iso*-Alloxazines, 7-amino-, synthesis of, 1926.
Allyl alcohol, addition of chlorine to, in hydrochloric acid, 1393.
Allyl compounds, 3-chloro-, 2180.
Allylcarbamic acid, methyl ester, 2320.
Allyl*di*chloroarsine, 3-chloro-, 2183.
Allylmalonic acid, esters, 663.
Almond-tree gum, structure of, 1677.
Alumina. See Aluminium oxide.
Aluminium, reaction of, with nitrosyl chloride, 1955.
Aluminium chloride, reaction of, with nitrosyl chloride, 1955.
oxide, catalytic, for vapour-phase reactions, 267.
γ-form, properties of, 267.
powder, calcined and hydrated, adsorption by, of *n*-heptoic acid, and specific surface measurement, 969.
Aluminosilicates, adsorption of, and their colour reactions, 2164.
mineral, 127.
Amides, 1081.
Amidines, 303, 1514, 1618.
chemotherapeutic, 261.
preparation of, from substituted amides, sulphonyl chlorides, and pyridine, 1618.
substituted, preparation of, 1514.
p-Amidinobenzyl methyl sulphide, acetate and hydrochloride, 1504.
p-Amidinobenzyl methyl sulphone, benzoate and hydrochloride, 1504.
2-Amidinopyridine, preparation of, 308.
Amidone, tetrahydrofurans related to, 1993.
Amines, aromatic, polycyclic, 1756.
containing 2-halogenoethyl groups, 2174.
formylation of, with ethyl formate, 1457.
molecular association of, from viscosity, 1345.
primary, secondary, and tertiary, physical properties and constitution of, 1825.
reaction of, with esters, 1989.
Amino-acids, bacteriostasis by, 85.
α-Amino-acids, degradation of, to aldehydes and ketones, 176.
synthesis of, 1386.
α-Amino-β-mercapto-acids, new synthesis of, 1337.
α-Amino-nitriles, reaction of, with *iso*thiocyanates, 1262, 2028.
Aminophosphonic acid, diethyl ester, 701.
Ammines, 1912.
Ammonia, equilibrium of, with sulphur dioxide and water, 76.
Ammonium sulphinates, action of chlorine on, in aqueous solution, 147.
n-Amyl nitrite, preparation and physical properties of, 1847.
*sec.-iso*Amyl iodide, olefin formation from, 2090.
2-*n*-Amyl-4-benzylaminomethylene-4:5-dihydro-oxazole, 5-amino-, 1971.
n-Amyldicyandiamide, 1633.
*sec.-iso*Amyldimethylsulphonium ions, olefin formation from, 2090.
tert.-Amyldimethylsulphonium salts, olefin formation from, 2084.
n-Amylmalonic acid, esters, 633.
α-*n*-Amyloenanthic acid, α-amino-, 1388.
2-*n*-Amyloxazole, 4-cyano-, synthesis of, 1969.
tert.-Amylsulphonium salts, olefin formation from, 2038.
p-*n*-Amylsulphonylbenzylammonium chloride, 382.
p-*n*-Amylsulphonylphenyl cyanide, 383.
2-*n*-Amylthioethanethiol, 1895.
Analgesics, new, 559.
synthetic, 2011.
Analysis, chromatographic, quantitative, of mixed sugars, 1679.
Androstan-17-on-3(β)-yl benzoate, 790.
Androst-5-ene-3(β):17(α)-and -3(β):17(β)-diols, dibenzoates, 791.
Androst-5-en-3(β)-ol-17-one, and its acetate and benzoate, 4-phenylsemicarbazones of, 790.
Anethole, dimerides of, 1984.
*iso*Anethole, and its isomers, 1984.
Anhydrides of polyhydric alcohols, 2201, 2204.
Anhydrohexitol, *di*chloro-, 2207.
1:4-Anhydrosorbitol, derivatives, from 1:4-3:6-dianhydrosorbitol, 237.
formation of, from glucamine, 299.
1:4-Anhydrosorbitol, 6-chloro-, and its derivatives, 240.
Anhydro-ψ-strychninenitromethane, 954.
Anhydro*neo*strychninephosphorous acid, 956.
Anhydro-ψ-strychninephosphorous acid, and its perchlorate, 955.
Aniline, diazotisation of, 558.
Aniline, 2-chloro-5-nitro-, thiolation of, 870.
5-Anilinoacridine, 5-*m*- and -*p*-nitro-, 1183.
6-Anilino*meso*benzanthrone, and 6-*p*-chloro-, and 6-*p*-nitro-, 1749.
6-Anilino-4-*n*-butylamino-1-*p*-chlorophenyl-1:2-dihydro-1:3:5-triazine-2-thione, 6-*p*-chloro-, 1642.
2-Anilino-4-carbethoxythiazole, 5-amino-, 2030.
4-Anilino-2-*p*-di-*n*-butylaminopropylaminoquinazoline, 4-*p*-chloro-, *di*hydrochloride, 1771.
2-Anilino-4-β-diethylamino-6:7-benzoquinazoline, 2-*p*-chloro-, *di*hydrochloride, 1766.
2-Anilino-4-β-diethylaminoethylamino-6:7-dimethoxyquinazoline, 2-*p*-chloro-, *di*hydrochloride, 1766.
2-Anilino-4-β-diethylaminoethylamino-5-, -6-, -7-, and -8-methoxyquinazolines, 2-*p*-chloro-, *di*hydrochlorides, 1766.
2-Anilino-4-β-diethylaminoethylamino-7-methylquinazoline, *di*hydrochloride, 1766.
4-Anilino-1-β-diethylaminoethylaminophthalazine, and 4-*p*-chloro-, 780.
2-Anilino-4-β-diethylaminoethylaminoquinazoline, 6- and 7-amino-2-*p*-chloro-, hydrochlorides, 1766.
6-chloro-2-*p*-chloro-, 6- and 7-nitro-2-*p*-chloro-, and their hydrochlorides, 1765.
4-Anilino-2-β-diethylaminoethylaminoquinazoline, 4-*p*-chloro-, salts, 1770.
2-Anilino-3-β-diethylaminoethylaminoquinoxaline, 2-*p*-chloro-, 781.
4-Anilino-1-δ-diethylamino-α-methyl-*n*-butylaminophthalazine *di*picrate, 780.
4-Anilino-1-γ-diethylaminopropylaminophthalazine, and 4-*p*-chloro-, 780.
4-Anilino-2-γ-diethylaminopropylaminoquinazoline, 4-*p*-chloro-, 1770.
2-Anilino-3-γ-diethylaminopropylaminoquinoxaline, 2-*p*-chloro-, 781.
2-Anilino-4-β-diethylaminoquinazolines, 2-*p*-chloro-, nuclear substituted, 1759.

4-Anilino-6-dimethyldihydro-1:3:5-triazine, 2-amino-4-*p*-chloro-, 1655.
4-Anilinodiphenyl, 3-nitro-, 222.
4-Anilino-4-methylamino-1:2-dihydro-1:3:5-triazine-2-thione, 6-*p*-chloro-, 1642.
4-Anilino-3-methylcinnoline, 358.
4-Anilino-7-methylcinnoline, 8-nitro-, 1705.
4-Anilino-8-methylcinnoline, and nitro-, 1706.
4-β-Anilinomethylenedihydro-β-quinindene methiodide, 1897.
Anilinomethylenemalonic acid, *p*-amino-, acetyl derivative, diethyl ester, 893.
Anilinomethyl ethyl ketone, and its semicarbazone, 275.
Anilinomethyl *n*-propyl ketone, 277.
4-Anilino-1-methylquinazoline, 6- and 7-amino-, salts, 365.
1-Anilinonaphthalene, 1-(2′-amino)-, and 1-(2′-nitro)-, 222, 223.
2-amino-, and 2-nitro-, 221, 222.
2-Anilinonaphthalene, 2-(2′-amino)-, and 2-(2′-nitro)-, 223.
4-Anilino-2-naphthoic acid, 3-*m*- and -*p*-nitro-, 1294.
4-Anilino-4-phenylthiazole, 5-amino-, 1266.
4-Anilino-5-phenylthioureidothiazole, 1267.
4-Anilinophthalazine, 1-chloro-, and 1-chloro-4-*p*-chloro-, and their hydrochlorides, 779, 780.
4-Anilino-2-γ-piperidinopropylaminoquinazoline, 4-*p*-chloro-, and its dihydrochloride, 1771.
4-Anilino-4-*iso*propylamino-2-methoxy-1:3:5-triazine, 6-*p*-chloro-, 564.
4-Anilino-4-*iso*propylamino-1:3:5-triazine, 564.
4-Anilino-4-*iso*propylamino-1:3:5-triazine, 2-amino- and 2-chloro-6-*p*-chloro-, and their derivatives, 563.
2-chloro-, and 6-*p*-chloro-, 564.
4-Anilino-4-(2′-pyridylamino)-6-methylpyrimidine, 2-*p*-chloro-, and its dihydrochloride, 596.
4-Anilino-2-(2′-pyridylamino)-6-methylpyrimidine, 4-*p*-chloro-, and 4-*p*-nitro-, and their dihydrochlorides, 595, 596.
4-Anilinoquinazoline, 2:4-*p*-*di*chloro-, 1770.
6- and 7-nitro-, 364, 365.
4-Anilinoquinoline, 6-nitro-, 1708.
2-Anilinoquinoxaline, 6-chloro-3-amino-2-*p*-chloro-, 782.
2-Anilinoquinoxaline, 2-amino-3-*p*-chloro-, 781.
2-chloro-3-*p*-chloro-, 780.
4-Anilino-1:3:5-triazine, 2:4-*di*chloro-, 564.
2:4-*di*chloro-6-*p*-chloro-, 563.
4-Anilohexamethyleneimine, 1619.
and its hydrochloride, 1520.
4-Anilopentamethyleneimine, and its hydrochloride, 1520.
Anionotropic rearrangement, kinetics of, 794, 1982.
Anionotropic systems. See under Systems.
Anionotropy, mechanism of, 794.
4-*p*-Anisidinoacridine, 1183.
Anisole-2-sulphonamide, 4:5-*di*chloro-, 214.
Anisole-2-sulphonethylanilide, 3:4- and 5:5-*di*chloro-, 214, 215.
4-Anisylacetic acid, ethyl and methyl esters, preparation of, 153.
1-*p*-Anisylpyrrolidine, and its picrate, 187.
1-*p*-Anisyl-Δ³-pyrroline, and its picrate, 187.
Annual General Meeting, 539, 904.
Anomospermum grandifolium, curare from, 1945.
Anthranilic acid, 4-chloro- and 4-nitro-, preparation of, 1762.
Anthraquinone, derivatives, spectra of, infra-red, and structure, 1441.
Anthraquinone, 1:4:5:8-*tetra*amino-, methyl derivatives of, 736.
Anthraquinone-1-carboxylic acid, 4-bromo-, 1625.
5-chloro-, 1749.
Anthraquinone series, 1627.
Antibacterials, absorption of, by *Bacterium lactis aerogenes,* 2290.
Antimalarials, new, 123.
synthetic, 574, 581, 586, 594, 777, 1630, 1636, 1645, 1759, 1766.
chemistry of, 97, 561, 1719.
Antimalarial activity, constitution and, 1909.
Antimony *tri-* and *pent*-oxides, amphoteric properties and solubility of, 759.
Antimony electrodes. See under Electrodes.
9-L-Arabofuranosidamino-5-(2′:5′-*di*chlorobenzeneazo)-2-methylthiopyrimidine, 6-amino-, 964.
9-L-Arabofuranosido-2-methylthioadenine, synthesis of, 957.
9-L-Arabopyranosidamino-5-(2′:5′-*di*chlorobenzeneazo)-2-methylthiopyrimidine, 6-amino-, 964.
Areolatin, and its derivatives, and its dyeing properties, 569, 570.
synthesis of, and its isomer, 990.
Aromatic compounds, cationoid activity of, 1175, 1622, 1746.
kinetics of halogen substitution in, 100.
kinetics of sulphonation of, 1065.
new, attempts to prepare, 974.
transition state in substitution in, 727.
Arsacridine, derivatives of, 292, 295.
Arsacridinic acid, 3-chloro-, 298.
Arsanthren cyanide, 2212.
Aryl cyanides, condensation of chloral with, 2322.
nuclei, union of, 2213.
N^1-Aryl-N^3-alkyl-N^5-alkyl- and **-dialkyl-diguanides,** preparation of, 1636.
N^1-Aryl-N^5-alkyldiguanides, preparation of, 1630.
Aryl alkyl ketones, parachors and refractivities of, 610.
Arylamines, reaction of, with ethyl ethoxymethylenemalonate, 893.
Arylbeniminoquinolyl ethers, attempted rearrangement of, 1603.
Aryldiazoates, decomposition reactions of, 556.
2-Arylguanidino-4-aminoalkylaminopyrimidines, 574.
Arylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines, 2-substituted, 580.
4-Arylguanidino-2- and **-6-dialkylaminoalkylaminopyrimidines,** 586.
***p*-Arylsulphonylbenzaldehydes,** synthesis of, 601.
Aryl 2-thienyl sulphones, synthesis of, 525.
Atoms, non-bonded, reactions between, 340.
Auramine, nitration of, 2169.
4-Azabeniminazole, and 6-bromo-2-hydroxy-, and 2-hydroxy-, 1392.
4-Azabeniminazoles, 1389.
4-Azabeniminazole-2-thiol, and 6-bromo-, 1392.
4- and **5-Azaindoles,** synthesis of, and their derivatives, 198.
5-Azaquinoxaline, and 7-bromo-, and its *N*-oxide, 1391.
5-Azaquinoxalines, 1389.
Azeotropic systems, binary, composition, pressure, and temperature relationships in, 1987.
Azlactones from 2-nitro-derivatives of vanillin, *iso*vanillin, and veratraldehyde, 376.
***cis*-Azobenzene,** dipole moment of, and of benzocinnoline and its oxide, 1949.
properties of, 1097.
Azole series, 201, 1056, 1060, 1262, 1337, 1340, 2028, 2031.
Azo*iso*propane, thermal data for, 1190.
***cis*-Azoxybenzene,** dipole moment of, and of benzocinnoline and its oxide, 1949.
Azoxy-5-chloro-2-β-piperidinobutyramidobenzene, 1911.
Azulenes, 164.

B.

Bacteria, adaptation of, to acridine derivatives, 1235.
chemistry of, 1605.
coliform, growth of, in nitrate and nitrite media, 824, 833, 841, 845.
Bacteriostasis by amino-acids, 85.
Bacterium lactis aerogenes, cells, absorption of antibacterials by, 2290.
Balance sheets, 905.
Barbituric acid, condensation of, with isatin and 1-methylisatin, 552.
Barium bromo*tetra*fluoride, 2137.
Bases, cyclic, reduced, stereochemistry and synthesis of, 1373.
heterocyclic, strength of, 2240.
Beetroots, sugar, pectin, araban component of, 2311.
Benzacridine, derivatives, 123.
1:2-Benzacridine, 5-amino-, 1290.
7-amino-, 1294.
8-amino-, 1228.
4′:5-*di*amino-, and 4′-nitro-5-amino-, 1291.
5:8-*di*chloro-, 125.
2:3-Benzacridine, preparation of, 1294.
2:3-Benzacridine, 5-amino-, and its derivatives, 1290.
7-amino-, 1294.
3:4-Benzacridine, 5-amino-, 1291.
7-amino-, 1294.
8-amino-, 1228.
5:8-*di*chloro-, 126.

Benzacridine series, syntheses in, 1284.
2:3-Benzacridone, 7-nitro-, 1294.
Benzaldehyde, 4:5-*di*hydroxy-6-nitro-, bisbenzenesulphonyl derivative, 1246.
2-nitro-4:5-*di*hydroxy-, preparation of, 2224.
6:7-Benzalloxazine, 222.
Benzamidine, condensation of, with α-diketones, 731.
Benzamidine, 3:5-*di*nitro-, salts, 308.
8-Benzanilidoquinoline, and 5:7-*di*chloro-, 1604, 1605.
1:2-Benzanthracene, photo-polymerisation of, 2129.
1:2-Benzanthracene, 2′-amino-, 2′- and 3′-chloro-, and 3′-cyano-, 1758, 1759.
1:2-Benzanthraquinone, 2′-amino-, and 2′- and 3′-chloro-, 1758.
meso-**Benzanthrone**, 1175.
3-acyl and 3-aroyl derivatives, synthesis of, 2037.
meso-**Benzanthrone**, 3-amino-, and 2-nitro-3-amino-, and their 3-acetyl derivatives, and 2-hydroxy-, 1088, 1089.
6-amino-, and its 6-acetyl derivative, 6-hydroxy-, and 4-iodo-, 1179, 1180.
6-amino-, 6-bromo-, 6-chloro-, and 6-iodo-, and their derivatives, 1624.
6- and 8-chloro-, properties of, 1746.
4-fluoro-, 1626.
Benzene, and its deuterated derivatives, spectra of, absorption and fluorescence, 406, 491.
catalytic reaction of, with ethylene, 73.
*hexa*chloride. See *cyclo*Hexane, *hexa*chloro-.
excited states of, 406, 417, 427, 433, 440, 445, 456, 461, 475, 483, 491, 508.
methylation of, by dimethyl ether, 2154.
molecules, elastic constants of, 509.
reactions of, with acyl peroxides, 2217.
spectrum of, absorption, ultra-violet, 417.
fluorescence, ultra-violet, 427.
substitution in, ortho–para ratio in, 728.
Benzene, 1:2:3-*tri*amino-, *di*picrate, 2132.
chloro-, halogenation of acetone in, 370.
1-chloro-2:6-*di*nitro-, preparation of, 1008.
nitro-, sulphonation of, by sulphuric acid, 1065.
o- and *p*-*di*nitro-, preparation of, 1512.
Benzeneazoacetoacetyl chloride, 1925.
Benzeneazoacetoacetylethyleneimide, 1925.
2- and **6-Benzeneazo-3:4-diethylphenols**, 2- and 6-*p*-chloro-, 2146.
2- and **6-Benzeneazo-3:4-dimethylphenols**, 2- and 6-*p*-chloro-, 2146.
2- and **6-Benzeneazo-3-methyl-4-ethylphenols**, and 2- and 6-*p*-chloro-, 2146.
2- and **6-Benzeneazo-3-methyl-4-*n*-propylphenols**, 2- and 6-*p*-chloro-, 2146.
5-(Benzenesulphonamido)-2:6-dimethyl-3-pyridazone, 5-*p*-amino-, 5-*p*-acetyl derivative, 2197.
2-Benzenesulphonamido-4-hydroxy-6-methylpyrimidine, 2-*p*-amino-, 2-*p*-acetyl derivative, 147.
3-(Benzenesulphonamido)pyridazine, 3-*p*-amino-, 3-*p*-acetyl derivative, 2198.
Benzenesulphonic acid, *p*-hydroxy-, ammonium salt, 307.
Benzenesulphonyl-. See also Phenylsulphonyl-.
Benzenesulphonylacetylguanidine, *p*-amino-, and its *p*-acetyl derivative, and *p*-nitro-, 145, 146.
Benzenesulphonylacetylmethyl*iso*thiourea, *p*-amino-, *p*-acetyl derivative, 146.
Benzenesulphonylbenzoylguanidine, *p*-amino-, and *p*-nitro-, 147.
Benzenesulphonyldibenzoylguanidine, *p*-amino-, and *p*-nitro-, 147.
***N*-Benzenesulphonyl-*NN′*-dimethylacetamidine**, and its picrate, 1523.
Benzenesulphonylguanidine, *p*-amino-, acyl derivatives, 143.
***N*-Benzenesulphonyl-*N′*-methylacetamidine**, 1522.
***N*-Benzenesulphonyl-*N′*-phenylbenzamidine**, 1523.
Benzenesulphonylpropionylguanidine, *p*-amino-, *p*-acyl derivatives, 146, 147.
3:4-Benzfluorenones, 1231.
3:4-Benzfluorenone, 7-nitro-, 1235.
Benzhydryl dibenzyl phosphate, 1111.
Benzil, 2:4:6:2′:4′-*penta*nitro-, 1613.
Benziminazole, dissociation constants of, 765.
Benziminazoles, antimalarial activity and structure of, 1909.
Benzocinnoline, and its oxide, dipole moments of, 1949.
meso-**Benzodianthrone-6:6′-dicarboxylic acid**, 1625.
Benzo*tri*fluoride, and its fluoro-derivatives, spectra of, infra-red absorption, 1435.
Benzoic acid, allyl ester, addition of chlorine to, 1394.
Benzoic acid, *p*-amino-, derivatives of, 241.
Benzoin, condensation of, with quinol or resorcinol, 1992.
Benzophenone, action of potassium *tert.*-butoxide on, 1411.
oxime benzene- and *p*-toluene-sulphonates, 1517.
Benzophenone, 4:4′-*di*amino-, dibenzoyl derivative, 1459.
6:7-Benzoquinazoline, 2:4-*di*chloro-, and 2:4-*di*hydroxy-, 1765.
***p*-Benzoquinone**, condensation of, with 2:3-dimethyl-1:3-butadiene, 1499.
m- and *p*-**Benzotetraphenyldifurfurans**, 1992.
Benzo-1:3:5-triazepine, 2:4-*di*amino-, and its salts, 1371.
Benzoxazolone-7-sulphonic acid, 5:6-*di*chloro-, and its sodium salt, and 5-chloro-6-amino-, 214.
Benzoyl *per*oxide, *o*-nitro-, 2216.
***N*-Benzoyl-*N′*-acetyl-*N′*-methyl-*p*-phenylenediamine**, 1604.
3-Benzoyl*iso*amyl cyanide, 1743.
3-Benzoyl*meso*benzanthrone, 3-*o*-chloro-, 2038.
α-Benzoylbenzhydryl radical, anionic nature of, compared with cationoid reactivity of the triphenylmethyl radical, 1549.
Benzoylcyanamide, preparation of, 589.
1-Benzoyldiazoethane, 1-*p*-nitro-, 1675.
***N*-Benzoyldiphenylamine-3:3′-bisazo-β-naphthol**, 1006.
Benzoylethyleneimine, addition of hydrogen sulphide to, 1919.
preparation and reactions of, 1923.
3-Benzoyl-3-ethylhexanecarboxylic acid, 1744.
9-Benzoylhexahydrocarbazole, 11-nitro-10-hydroxy-, preparation and hydrolysis of, 2319.
Benzoylmalonic acid, ethyl ester, preparation of, 555.
3-Benzoyl-3-methylbutanecarboxylic acid, and its semicarbazone, 1743.
***N*-Benzoyl-4-methyldiphenylamine**, 2-bromo-, 1604.
3-Benzoyl-3-methylheptanecarboxylic acid, 1743.
3-Benzoyl-3-methylundecanecarboxylic acid, 1743.
***N*-Benzoyl-*N′*-phenylbenzamidine**, 1523.
***N*-Benzoyl-β-phenyl-*S*-benzylcysteine**, methyl ester, 1063.
β-Benzoylpropionic acid, α-cyano-, catalytic reduction of, 188.
5-Benzoyl 2:3-*iso*propylidene methyl-D-ribofuranoside, 962.
***N′*-Benzoylthioureidoacetamide**, 1265.
5-Benzoylthioureido-4-phenylthiazole, 2-amino-, 2-benzoyl derivative, 1266.
5-Benzoylthioureidothiazole, 2-amino-, 2-benzoyl derivative, 1265.
DL-***O*-Benzoylthreonine**, ethyl ester, salts, 317.
DL-***N*-Benzoyl*allo*threonine**, ethyl ester, 317.
DL-***N*-Benzoyl-*O*-*p*-tosyl*allo*threonine**, ethyl ester, 317.
5-Benzoyl 2:3:4-triacetyl L-arabinose, 963.
diethylthioacetal, 963.
5-Benzoyl 1:2:3-triacetyl D-ribose, 962.
1:2-Benzperylene, crystal structure of, 1398.
Benzquinoline series, syntheses in, 1284.
6:7-Benzquinoline, 3- and 4-amino-, 4-hydroxy-, and 3-nitro-, 1293.
3:4-*di*amino-, and its hydrochloride, and 4-chloro-3-nitro- and 3-nitro-4-amino-, 1289.
7:8-Benzquinoline, 2:4-*di*chloro-, 1292.
4-hydroxy-, 894.
7:8-Benzquinoline-3-carboxylic acid, 4-hydroxy-, ethyl ester, 894.
Benz-1-thia-2:3-diazole, derivatives of, 870.
nitration of, 1006.
Benz-1-thia-2:3-diazole, 5-bromo-, and 5-iodo-, 874.
5-hydroxy-, preparation of, 873.
5-nitro-, preparation of, 872.
7-nitro-, 1009.
Benz-1-thia-2:3-diazoles, 5-substituted, preparation of, 1002.
Benz-1-thia-2:3-diazole-5-azo-β-naphthol, 873.
Benzthiazole, 2-mercapto-, hydroxymethyl derivative of, 1717.
Benzthiazoles, 2-amino-, spectra of, absorption, ultra-violet, 1497.
8-Benz-*o*-toluididoquinoline, 1605.
Benzyl 2-aminoethyl sulphide, preparation of, 1925.
cyanide, α-amino-, thiocyanate, 1344.
methyl sulphide, *p*-cyano-, 1503.
2-Benzylaminonaphthalene, 1-amino-, 223.
Benzylaminophosphonic acid, dibenzhydryl ester, 1110.

2-Benzylamino-1-*p*-tolueneazonaphthalene, 223.
Benzyl-*n*-amylamine, and its hydrochloride, 97.
9-Benzyl-5:6-benzo*iso*alloxazine, 223.
1-Benzyl-4-benzylidene-2-thiohydantoin, 1064.
2-Benzylcarbamylphenylthioacetic acid, and its *N*-benzylimide, 84.
***N*-Benzyl-*p*-chloroaniline**, 297.
5-Benzyldialuric acid, 556.
Benzyldi-*n*-amylamine, 97.
5-Benzylideneamino-2-carbethoxyamino-4-phenylthiazole, 1343.
Benzylidene anhydrohexitol, chloro-, 2207.
3:5-Benzylidene 1:4-anhydrosorbitol, constitution of, and 6-iodo-, 299, 302.
3:5-Benzylidene 1:4-anhydrosorbitol, 6-bromo-, 2203.
6-chloro-, 239.
Benzylideneanil, thermal data for, 1190.
3′:5′-Benzylidene cytidine, and its tetraphenyl-N^6:2′-diphosphate, 1530.
Benzylideneguanosine, and its acetyl derivative, 1380.
5-Benzylidene-3-methyl-2-thiohydantoin, 2029.
Benzylideneoxindole, 2′:5-*di*nitro-, 924.
Benzylidenerhodanines, bromo-, and chloro-, 1253.
4-Benzylidenethiazol-5-one, 2-mercapto-, 204.
Benzylmalonic acid, amino-*p*-cyano-, acetyl derivative, ethyl ester, 87.
Benzylmalonic dideuteracid, 1087.
3-Benzyl-3-methylheptanecarboxylic acid, and its *S*-benzylthiouronium salt, 1743.
9-Benzyl-10-methylphenanthridinium halides, 7 : 9-*p*-*di*amino- and 7-amino-9-*p*-nitro-, and their acetyl derivatives, 196.
salts, 9-*p*-amino-, and 9-*p*-nitro-, 196.
4-*O*-Benzyl-5-methylresorcylaldehyde, 2258.
Benzyl methyl sulphone, *p*-cyano-, 1504.
3-Benzyl-3-methylundecanecarboxylic acid, and its *S*-benzylthiouronium salt, 1744.
***p*-Benzyloxyphenylpyruvic acid**, 260.
9-Benzylphenanthridine, 7-amino-9-*p*-nitro-, and its acetyl derivative, and 9-*p*-nitro-, 195, 196.
9-*p*-nitro-, 196.
Benzylphosphonic acid, diethyl ester, 702.
***S*-Benzyl-*N*-*iso*propylthiobenzamide**, and its picrate, 1924.
***p*-Benzylsulphonylbenzylammonium** chloride, 382.
***N*-Benzylsydnone**, and nitroso-, 2309.
β-Benzylthioacrylic acid, α-amino-, hexoyl derivative, and its ethyl ester, 1968.
β-Benzylthioacrylylbenzamide, α-amino-, benzoyl and hexoyl derivatives, 1969.
2-Benzylthio-4-anilinomethylenethiazolone, 1059.
2-Benzylthio-4-benzylidenethiazolone, 1060.
***N*-Benzylthiocarbamidoglycine** benzylamide, 1058.
2-Benzylthio-4-carboxythiazole, 1059.
β-Benzylthio-α-carboxy*iso*valeric acid, 1685.
2-Benzylthio-4-ethoxymethylenethiazolone, 1059.
2-Benzylthio-4-hydroxymethylenethiazolone, 1059.
2-Benzylthiothiazole, 5-amino-, and its hydrobromide, 205.
2-Benzylthiothiazolone, and its hydrobromide, 1058.
β-Benzylthio*iso*valeric acid, α-nitro-, ethyl ester, 685.
2-2′-Benzylthiovinylbenzthiazole methiodide, 689.
DL-*N*-Benzyl*allo*threonine, 316.
α-Benzyl-*n*-valeramide, 1676.
Betacoccus arabinosaceous, dextran synthesis from sucrose by, 1555.
Betulinic acid, and its derivatives, from plane tree bark, 948.
Betulinic acid, bromo-, and its acetyl derivative, and its derivatives, 950.
4:6-Bisacetamidoquinoline, and its salts, 1709.
Bisanhydro*neo*strychninephosphoric acid, 956.
***NN′*-Bis-4-bromophenylacetamidine**, and its benzenesulphonate, 1520.
***meso*-*pp′*-Biscarbethoxyamino-3:4-diphenyl-*n*-hexane**, 687.
Bis-(6-chloro 3:5-benzylidene 1:4-anhydrosorbitol) 2:2′-sulphite, 301.
Bis-(*m*-chlorocinnamic acid) α-*di*sulphide, 1254.
2:5-Bischloromethyltetrahydrofuran, 157.
2:4-Bis-*p*-chlorophenylthioquinazoline, 1772.
Bis-*p*-cyanophenyl *di*sulphoxide, 382.
3-(Bis-*o*-cyanophenylthioacetyl)amino-2-6′-ketothionaphthene-(2″:3″:5′:4′)-1:3-oxasinyl-2′-thionaphthen, 80.
αα′-Bisdiazoacetyl-3:4-diethyl-1-*iso*propyl*cyclo*pentane, 168.
2:4-Bis-β-diethylaminoethylaminoquinazoline, and its salts, 1771.
2:5-Bis(diethylaminomethyl)tetrahydrofuran, and its methiodide, 158.
Bisdihydro*neo*strychninephosphoric acid, 956.
3:4-Bis-(3′:4′-dimethoxyphenyl)-*n*-hexane, 890.
6:6′-Bisdimethylamino-4:4′-dimethyl-2:2′-dipyrimidylamine, 596.
Bisdimethylaminofluorophosphine oxide, 1315.
4:6-Bis-(4-dimethylaminostyryl)pyrimidine, 2-chloro-, 2150.
2-hydroxy-, 2150.
2:5-Bisethoxymethyltetrahydrofuran, 158.
[Bis-2-(3-ethylbenzoxazole)][γ-2′-(3-ethylbenzoxazole)]pentamethincyanine *di*iodide, 694.
[Bis-2-(3-ethylbenzthiazole)]-α-anilomethyltrimethincyanine iodide, 1884.
[Bis-2-(3-ethylbenzthiazole)][αβ′-dimethin-2′-(3′-ethylbenzselenazole)]trimethincyanine *di*iodide, 1886.
[Bis-2-(3-ethylbenzthiazole)][γ-2′-(3-ethylbenzoxazole)]pentamethincyanine *di*iodide, 695.
[Bis-2-(3-ethylbenzthiazole)][γ-2′-(3-ethylbenzthiazole)]pentamethincyanine *di*iodide, 694.
Bis-[4′-ethyl-3-(dihydro-β-quinindene)]methincyanine iodide, 1897.
[Bis-2-(3-ethyl-Δ²-thiazoline)][αβ′-dimethin-2′-(3′-ethylbenzthiazole)]trimethincyanine *diper*chlorate, 1886.
2-Bis-(2-hydroxyethyl)amino-4-(4-dimethylaminostyryl)-6-methylpyrimidine, 2151.
2:5-Bishydroxymethyltetrahydrofuran *p*-toluenesulphonate, 156.
3:4-Bis-(3′:4′-*di*hydroxyphenyl)-*n*-hexane, and its acetyl and benzoyl derivatives, 890.
Bismethanesulphonyl dianhydrohexitols, 2206.
2:5-Bismethanesulphonyl 1:4-3:6-dianhydromannitol, 2208.
2:5-Bismethanesulphonyl 1:4-3:6-dianhydrosorbitol, 302.
4:5-Bis(methoxymethoxy)benzaldehyde, 2-nitro-, 1246.
1:5-Bismethylaminoanthraquinone, 4 : 8-*di*amino-, 4 : 8-*di*bromo-, 4:8-*di*nitro-, and *tetra*nitro-, 738.
1:8-Bismethylaminoanthraquinone, and 4:5-*di*amino-, and 4:5-*di*bromo-, 739.
Bis-[4-methyl-3′-(dihydro-*p*-quinindene)]methincyanine iodide, 1897.
***p*-Bismethylsulphonylbenzene**, 605.
4:4′-Bismethylsulphonyldiphenyl sulphide, 605.
*di*sulphide, 605.
4:4′-Bismethylsulphonyldiphenyl sulphone, 605.
1:10-Bis-2′-*p*-methylsulphonylphenyl-4′-thiazolyl-*n*-decane, 1508.
1:8-Bis-2′-*p*-methylsulphonylphenyl-4-thiazolyl-*n*-octane, 1507.
[Bis-2-(3-methyl-Δ²-thiazoline)]-α-anilomethyltrimethincyanine *per*chlorate, 1885.
5-Bisnitroaminoethane, crystal structure of, 1316.
4-Bis-(3′:5′-*di*nitro-4′-methylnitroaminophenyl)methylene-*N*-methylsemiquinone, 2:6-*di*nitro-, 2170.
4:4-Bisnitroxymethyloxazolidine, 3-nitro-, 1907.
***s*-Bis-(1-phenylpropyl)hydrazine**, *pp′*-*di*amino-, *pp′*-diacetyl derivative, 685.
Bisphenylsulphonyl sulphide, crystal structure of, 325.
*tri*sulphide, crystal structure of, 326.
Bisquindolinoyl, quaternisation of, 921.
4:5-Bis-*p*-toluenesulphonamido-1:8-bisdimethylaminoanthraquinone, 739.
Bis-*p*-tolylsulphonyl sulphide, and *tri*sulphide, crystal structure of, 326, 327.
***NN′*-Bis[tri(carbethoxyaminomethyl)methyl]urea**, 1906.
Bistriethyl-lead fluorophosphonate, 703.
Bonds. See Linkings.
Brassylic acid, α-amino-, and its α-acetyl derivative, 1388.
Bromine *tri*fluoride, reactions of, with carbon tetrahalides and with tetraiodoethylene, 2188.
with metallic halides, 2135.
Hydrobromic acid, oxidation of, by chromic acid in presence of manganous sulphate, 1376.
Brucine, 703, 951.
N-oxide, action of potassium chromate on, 704.
Buta-1:3-diene, 1-cyano-, reactions of, 227, 232.
Butane, 2:3-amino-, and its salts, 60.
2:2:3:3-*tetra*chloro-1:1:4:4-*tetra*amino-, 1:1:4:4-tetrabenzoyl derivative, 2322.
1-nitro-, preparation and physical properties of, 1847.
1:2-*di*nitro-, 59.

isoButane, 1:2-*di*nitro-, 56.
***cyclo*Butanecarboxylic acid**, preparation of, and its esters, 1806.
***cyclo*Butane-1:1-dicarboxylic acid**, preparation of, and its esters, 1806.
***tert.*-Butanol**, nitro-, 56.
Butan-2-one, *hepta*chloro-, 281.
2′-*n*-Butoxydiethyl sulphide, 2-chloro-, 2179.
6-*n*-Butoxynicotinamide, 1945.
6-*n*-Butoxynicotinamidine, hydrochloride and benzoate, 1945.
2-*n*-Butoxypyridine, 5-cyano-, 1945.
5-(2-*n*-Butoxypyridyl)methylamine *di*hydrochloride, 1945.
***n*-Butylamine**, adsorption of, from aqueous solutions by charcoal, 1483.
2-*n*-Butylanthraquinone, 1-amino-, 1:5- and 1:8-*di*amino-, 1-bromo-, *di*bromo-, 4-bromo-1-amino-, 1-chloro-, 1-nitro-, 1:5- and 1:8-*di*nitro-, and their derivatives, 1629.
2-*tert.*-Butylanthraquinone, 1-amino-, 1:5- and 1:8-*di*amino-, 4-bromo-1-amino-, *tri*bromo-, 4:6:8-*tri*bromo-1:5-*di*amino-, 1-nitro-, and 1:5- and 1:8-*di*nitro-, and their derivatives, 1628.
Butylanthraquinones, amino-, and nitro-, 1627.
4-Butylbenzyl cyanide, 4-chloro-, and 4-hydroxy-, and its α-naphthylurethane, 809.
***n*-Butyl*iso*butylideneamine**, thermal data for, 1190.
***tert.*-Butylcarbamic acid**, *s-tri*chloro-, methyl ester, 2320.
2-*iso*Butylcinchoninic acid, 6-bromo-, 108.
6:8-*di*chloro-, 109.
2-*n*-Butyldi-1:1′-anthraquinonylimide, 1629.
Butyldicyandiamides, 1633.
***n*- and *iso*-Butyldimethylsulphonium** salts, olefin formation from, 2072.
***sec.*-Butyldimethylsulphonium** salts, olefin formation from, 2077.
***tert.*-Butyldimethylsulphonium** salts, olefin formation from, 2084.
Butylenes, addition to, of dinitrogen tetroxide, 52.
2-Butylene, 2-nitro-, 60.
***iso*Butylenediamine**, *di*hydrochloride, 57.
2-(*N*³-*n*-Butylguanidino)-5:6-dimethoxybenziminazole, and its salts, 1370.
***N*-Butylguanylthiourea**, 1654.
2-*iso*Butylquinoline, 6-bromo-, and its picrate, 6-bromo-4-hydroxy-, and 6:8-*di*chloro-4-hydroxy-, 109.
4-hydroxy-, 108.
β-*n*-Butylsuccinic acid, α-amino-, 1388.
***tert.*-Butylsulphonium** salts, olefin formation from, 2038.
***p*-Butylsulphonylbenzylammonium** chlorides, 382.
2′-*n*-Butylsulphonyldiethyl sulphone, 2-chloro-, 2179.
***p-sec.*-Butylsulphonylphenyl** cyanide, 383.
2-*n*-Butylsulphonylpyridine, 5-amino-, and 5-nitro-, 1944.
2′-*n*-Butylthiodiethyl sulphide, 2-chloro-, 2179.
2-*n*-Butylthiopyridine, 5-amino-, and its hydrochlorides, and 5-nitro-, 1944.
But-3-yne-1-carboxylic acid, esters, 677.
Butyranilide, *p*-chloro-*o*-nitro-β-bromo-, 1911.
Butyric acid, α-amino-β-hydroxy-, preparation of, 316.
***iso*Butyric acid**, α-bromo-, and α-fluoro-, methyl esters, 1777.
Butyrophenone, *o*-amino-, and its acetyl derivative, 2318.
Butyrylpyruvic acid, β-hydroxy-, ethyl ester, 1297.
***N*-Butyryl-*p*-toluenesulphonamide**, 112.

C.

***iso*Cadinene**, spectrum of, absorption, 1306.
Carbamic acid, esters, molecular association in, 874.
4-Carbamido-1-methylglyoxaline, 5-amino-, and 5-amino-2-mercapto-, 2030.
Carbamylmethyldithiocarbamic acid, benzyl and carbamylmethylammonium esters, 204.
2-Carbamylphenylsulphinylacetic acid, 83.
2-Carbamylphenylsulphonylacetic acid, 83.
2-Carbamylphenylthioacetic acid, and its ethyl ester, and derivatives, 83, 84.
6-Carbamyl-3-pyridazone, 2197.
***S*-(5-Carbamyl-2-pyridyl)thiuronium chloride**, 1942.
2-(2′-Carbamyl-3′-thionaphthenyl)carbamylthionaphthen, 3-amino-, 3-acetyl derivative, 80.
Carbanilic acid, 3-chloroallyl ester, 2182.
Carbazoles, 919, 922.
2-Carbethoxyamino-5-acetamidothiazole-4-carboxylic acid, ethyl ester, 1344.
4(or 5)-Carbethoxyamino-2-acetylthioglyoxaline, 1342.
7-Carbethoxyamino-9-*p*-aminobenzyl-10-methylphenanthridinium chloride, 196.
9-*p*-Carbethoxyaminobenzyl-10-methylphenanthridinium bromide, 7-amino-, 7-acetyl derivative, 196.
chloride, 7-amino-, and its acetyl derivative, 196.
7-Carbethoxyamino-9-*p*-carbethoxyaminobenzyl-10-methylphenanthridinium chloride, 196.
2-Carbethoxyamino-5-carbethoxythioureido-4-methylthiazole, 1342.
2-Carbethoxyamino-5-carbethoxythioureido-4-phenylthiazole, 1343.
2-Carbethoxyamino-5-carbethoxythioureidothiazole-4-carboxylic acid, ethyl ester, 1344.
2-Carbethoxyamino-9:10-dimethylphenanthridinium bromide, 192.
3′-Carbethoxyaminodiphenyl, 2-amino-, and its acetyl derivative, 194.
4-Carbethoxyaminodiphenyl, 2-amino-, 2-acetyl derivative, 2-nitro-4′-amino-, and its 4′-acetyl derivative, and 2-nitro-, 192.
2-*p*-nitroamino-, benzoyl derivative, 193.
4(or 5)-Carbethoxyamino-2-mercaptoglyoxaline, 1342.
5-Carbethoxyamino-2-mercapto-4-methylglyoxaline, 1342.
5-Carbethoxyamino-2-mercapto-4-phenylglyoxaline, 1343.
5-Carbethoxyamino-4-methylglyoxaline, 1343.
2-Carbethoxyamino-9-methylphenanthridine, and its hydrochloride, 192.
6- and 8-Carbethoxyamino-9-methylphenanthridines, and their sulphates, 194.
2-Carbethoxyamino-4-methylthiazole, 5-amino-, 1342.
3-Carbethoxyamino-2′-*p*-nitrobenzamidodiphenyl, 194.
7-Carbethoxyamino-9-*p*-nitrobenzyl-10-methylphenanthridinium salts, 196.
7-Carbethoxyamino-9-*p*-nitrobenzylphenanthridine, 195.
4-Carbethoxyamino-2′-*p*-nitrophenylacetamidodiphenyl, 195.
2-Carbethoxyamino-9-*p*-nitrophenyl-10-methylphenanthridinium chloride, 193.
8-Carbethoxyamino-9-*p*-nitrophenyl-10-methylphenanthridinium chloride, 195.
2-Carbethoxyamino-9-*p*-nitrophenylphenanthridine, 193.
6- and 8-Carbethoxyamino-9-*p*-nitrophenylphenanthridines, 194.
5-Carbethoxyamino-4-phenylglyoxaline, 1343.
9-*p*-Carbethoxyaminophenyl-10-methylphenanthridinium bromide, 2-amino-, 193.
chloride, 2-amino-, 2-acetyl derivative, and 7-amino-, 193.
2-Carbethoxyamino-4-phenylthiazole, 5-amino-, 1343.
2-Carbethoxyaminoquinoxaline-3-carboxyamide, 518.
2-Carbethoxyaminothiazole, 5-amino-, and its 5-acetyl derivative, 1342.
2-Carbethoxyaminothiazole-4-carboxylic acid, 5-amino-, ethyl ester, salts, 1344.
***p*-Carbethoxybenzylacetoacetic acid**, ethyl ester, 1554.
4-ω-Carbethoxy-*n*-butylthiazole, 5-amino-2-mercapto-, 2033.
2-Carbethoxycoumarone, 2-hydroxy-, and its acetate, 2257.
4-Carbethoxy-2:5-diphenylthiazole, 1064.
2-Carbethoxy-6-hexahydrobenzyloxycoumarone, 2257.
2-Carbethoxyimino-3-acetyl-4-phenylthiazoline, 5-amino-, 5-acetyl derivative, 1343.
α-Carbethoxy-β-2-keto*cyclo*hexyl-β-phenylpropionamide, 2015.
4-Carbethoxy-1-methylglyoxaline, 5-amino-, and 5-amino-2-mercapto-, and their derivatives, 2030.
β-Carbethoxy-β-(2-methyl*cyclo*hex-1-enyl)propionic acid, 164.
3-Carbethoxy-5-methylquinoxaline, 2-hydroxy-, 2133.
***N*-Carbethoxy-*S*-methyl*iso*thioureidocarbethoxyacetonitrile**, 1344.
***p*-Carbethoxyphenylcarbamic acid**, ethyl and methyl esters, 878.
DL-*trans*-4-Carbethoxy-2-phenyl-5-methyl-Δ²-oxazoline, and its hydrochloride, 317.
4-Carbethoxy-5-phenylthiazole, 2-amino-, and its picrate, 1063.
2-Carbethoxythio-4-benzylidenethiazol-5-one, 1065.
2-Carbethoxythio-4-ethoxymethylenethiazolone, 1060.
α-Carbethoxythioureidobenzyl cyanide, 1343.
Carbethoxythioureidocarbethoxyacetonitrile, 1344.
Carbethoxythioureidocarbomethoxyacetonitrile, 1344.
α-Carbethoxythioureidopropionitrile, 1342.

3-Carbethoxy-o-tolyloxyacetic acid, ethyl ester, 1673.
ω-Carbethoxy-n-valeraldehyde cyanohydrin, 2032.
α-Carbethoxyisovaleric acid, β-mercapto-, ethyl ester, 1684.
Carbocyanines, unsymmetrical, preparation of, 687.
Carbohydrates, periodate oxidation applied to, 992.
Carbolines, 919, 922.
3-Carbomethoxy-6-benzyloxybenzaldehyde, 2-hydroxy-, and its 2:4-dinitrophenylhydrazone, 116.
3-Carbomethoxy-2:6-dibenzyloxybenzaldehyde, and its 2:4-dinitrophenylhydrazone, 116.
***N*-Carbomethoxydi-(2-chloroethyl)amine,** 2174.
2-Carbomethoxyphenylcarbamic acid, 4-bromo-, ethyl ester, 878.
Carbon atoms, saturated, substitution at, 1283.
compounds, thermochemical evaluation of bond strengths in, 1161.
deposition of, on vitreous silica, 1362.
rings, three- and four-membered, physical properties and constitution of, 1804.
five- and six-membered, physical properties and constitution of, 1809.
Carbon *tetra*halides, reaction of, with bromine trifluoride, 2188.
*di*oxide, conversion of, into acetylene, 1534.
*di*sulphide, reaction of, with aminoacetonitrile, 201.
with α-methylamino-nitriles, 1619.
Carbon–iodine linkings, evaluation of strength of, 1161.
Carbon–magnesium linkings, evaluation of strength of, 1161.
Carbon–nitrogen linkings, heat of formation of, 1187.
Carbonyl chlorofluoride and fluoride, preparation and reactions of, 2183.
compounds, reaction of, with α-amino-acids, 176.
groups, vibration frequency of, in infra-red absorption spectra, 1436.
o-Carboxyacetophenone 2′:4′:6′-*tri*bromophenylhydrazone, 600.
2-chloro-5-nitrophenylhydrazone, 209.
2′-chlorophenylhydrazone, 1029.
N^4-Carboxyacylsulphonamides, preparation of, 821.
3-Carboxyamidoquinoline-4-carboxylic acid, 2-hydroxy-, ethyl ester, 554.
o-Carboxybenzaldehyde α-acetylhydrazone and 2′-chlorophenylhydrazone, 1028.
2′:4′:6′-*tri*bromophenylhydrazone, 599.
2-chloro-5-nitrophenylhydrazone, 209.
3′-Carboxy-1:2-benzanthracene, 1759.
5-(p-Carboxybenzyl)-4-methyliminazol-2-one, 1554.
3-Carboxy-6-benzyloxybenzaldehyde, 2-hydroxy-, 116.
2-Carboxycoumarone, 6-hydroxy-, acetate, 2257.
4′-Carboxydiphenylamine, 4-amino-, and 4-nitro-, 241.
Carboxydiphenylarsonous acids, 2209.
4-Carboxy-2:5-diphenylthiazole, 1064.
4-Carboxy-2:5-diphenylthiazolidine hydrochloride, 1065.
DL-5-(p-Carboxyhexahydrobenzyl)-4-methyliminazolid-2-one, 1554.
***N*-4-Carboxymethoxy-3-methyl-1-naphthylglycine,** ethyl ester, 184.
11-Carboxy-5-methylquindoline, chloride and 5-methosulphate, 921.
6-Carboxyphenylacetoacetic acid, 2:4-*di*nitro-, ethyl ester, and its derivatives, 1718.
1-(p-Carboxyphenyl)-n-butane-2:3-dione 2-phenylhydrazone, 1554.
4-Carboxy-5-phenyl-2:2-dimethylthiazolidine hydrochloride, 1065.
N^1-m-Carboxyphenyl-N^5-*iso*propyldiguanide hydrochloride, 1635.
***N*-o- and -p-Carboxyphenylsydnones,** 2310.
4-Carboxy-5-phenylthiazole, 2-amino-, 1064.
4-Carboxy-5-phenyl-2-thiazolidone, 1064.
2-Carboxyphenylthioacetanilide, 83.
2-Carboxyphenylthioacetbenzylamide, 83.
4-Carboxy-5-phenyl-2-thiothiazolidone, 1064.
4-Carboxyquinoline-3-carboxyamide, 2-hydroxy-, 554.
2-Carboxythionaphthen, 3-amino-, and its *N*-acetyl derivative, 84.
2-(2′-Carboxy-3′-thionaphthenyl)carbamylthionaphthen, 3-amino-, and its derivatives, 80.
α-Carboxyisovaleric acid, β-mercapto-, and its calcium salt, 1684.
Carcinogenics, hydrocarbon, oxidation of, with osmium tetroxide, 170.
Carob bean. See *Ceratonia siliqua*.
Carob gum, galactomannan from, 1278.
mannose from, 1989.
β-Carotene, oxidation products of, and their *X*-ray structure, 710.
Catalysis, acid-base, in non-aqueous solvents, 370.
Catalysts, alumina, for vapour-phase reactions, 267.
alumina–silica, for reaction of naphthalene with methanol, 804.
for reaction of benzene with ethylene, 74.
Friedel–Crafts, cross-linking of vinyl polymers by, 771.
poisons for, detoxication of, 1091, 1093, 1916.
pyridine as poison for, 1095.
thoria, preparation of, 612.
Catalytic reactions, gas-phase, of aromatic hydrocarbons, 73, 1700, 2154.
vapour-phase, alumina catalysts for, 267.
(−)-*epi*Catechin, and its gallate, 2252, 2253.
Catechins from green tea, 2249.
Cellulose, oxidation of, by dinitrogen tetroxide, 1135.
Ceratonia siliqua, carob gum from, 1989.
Cerium salts, separation of, from neodymium salts, by ion exchange, 1272.
Chabazite, adsorption of gases on, 135.
mineral with sorptive properties like, 127.
Charcoal, adsorption by, from aqueous solutions, 1483.
columns, adsorption by, from aqueous solutions, 1487.
Chemotherapeutics, amidine, 261.
sulphone type, 1501, 1506, 1939.
Chloral, condensation of, with aryl cyanides, 2322.
Chlorine, action of, on ammonium sulphates, in aqueous solution, 147.
Hydrochloric acid, dissociation of, in oxygen-containing solvents, 1971.
Cholestane, 3(α)-chloro-, and 3(β)-hydroxy-, preparation of, 1040.
Cholestane-6||7-dicarboxylic acid, 3(α)- and 3(β)-hydroxy-, and their derivatives, 1040, 1041, 1042.
Cholestan-7-on-3(β)-yl benzoate, 792.
Cholest-2-(or 3)-ene-6||7-dicarboxylic anhydride, 1041.
Cholest-6-ene-3(β):5(α)-diol, 1796.
Cholest-6-en-5(α)-ol, 3-β-hydroxy-, acetyl and benzoyl derivatives, 1796.
Cholesterol, stereochemistry of, 1032.
7-substituted derivatives of, 1788, 1792, 1798.
Cholesterol, "α"-and "β"-7-hydroxy-, acetyl derivatives, 1797.
Cholesterols, 7-hydroxy-, epimeric, esters, 1792.
Cholesteryl acetate, "β"-7-chloro-, and -iodo-, 1792.
benzoate, "β"-7-bromo-, -7-chloro-, and -7-iodo-, 1792.
"α"-7-chloro-, 1792.
bromide, preparation of, 1787.
bromide and chloride, "β"-7-bromo-, 1787.
esters, "β"-7-bromo-, 1786, 1787.
bromo-, chloro-, and hydroxy-, and their acyl derivatives, 1795.
fluoroacetate, 1779.
Chondrodendron tomentosum, curare from, 1945.
Chromatography, partition, of mixed sugars, 1679.
Chromic acid. See under Chromium.
Chromium :—
Chromic acid, oxidation by, mechanism of, 1666.
of hydrobromic acid in presence of manganous sulphate, 1376.
Dichromates, photochemical oxidation with, 2119.
Chrysene, synthesis of, and its derivatives, 999.
Cinnamaldehyde, p-nitro-, *di*nitrophenylhydrazone, 2011.
Cinnamic acid, α-amino-, α-acetyl derivative, methyl ester, 1063.
Cinnamyl halides, coupling reaction of, 1111.
Cinnoline, 4-amino-, 1713.
4-amino-, 6- and 7-chloro-4-amino-, 6-nitro-4-amino-, and their acetyl derivatives, 360.
3-bromo-4-hydroxy-, and 3-chloro-4-hydroxy-, and their acetyl derivatives, 1173.
3:6-*di*bromo-4-hydroxy-, 3-chloro-6-bromo-4-hydroxy-, 6-chloro-3-bromo-4-hydroxy-, and 3:6-*di*chloro-4-hydroxy-, and their 4-acetyl derivatives, 1174.
8-nitro-4-amino-, 1705.
Cinnolines, 354, 358, 1170, 1702, 2318.

Cinnolines, 4-amino-, preparation of, 358.
3-halogeno-4-hydroxy-, preparation of, 1170.
3-3′-Cinnolyl-*n*-propane-1-carboxylic acid, 3-4′hydroxy-, 2319.
Citraconic acid, esters, 665.
Citral, spectrum of, infra-red absorption, 1414.
Citronellal, spectrum of, infra-red absorption, and structure, 1414.
Citronellol, spectrum of, infra-red absorption, and structure, 1413.
Clathrate compounds, 61, 571, 815.
Coal, bituminous, *X*-ray diffraction and solvent extraction studies of, 1693.
Compounds, molecular, structure of, 61, 571, 815.
Constitution, antimalarial activity and, 1909.
physical properties and, 607, 610, 616, 624, 644, 654, 658, 674, 1804, 1809, 1814, 1820, 1825, 1833.
Copper, oxide-film formation on, and its potential, 740.
Copper electrodes. See under Electrodes.
Coprosma, chemistry of, 564, 568, 990.
Coprosma areolata, colouring matters from, 568.
Coprosma australis, colouring matters from, 564.
Cortex piscidiæ erythrinæ, constituents of, 257.
Coumarin, 5-nitro-3-hydroxy-, 1609.
Coumarins, 4-hydroxy-, synthesis of, 174.
Coumarin-3-carboxylic acid, 2257.
Coumarone, 6-hydroxy-, 6-benzyl derivative, and *p*-nitrobenzoate, 2257.
β-Coumarone-5-acrylic acid, β-6-hydroxy-, 6-acetyl derivative, and its 2:4-dinitrophenylhydrazone, 2258.
Coumarone-2-carboxylic acid, 6-hydroxy-, 6-benzyl derivative, ethyl ester, 2257.
Coumarono-(2′:3′:3:4)-coumarins, 1672.
Coumarono-(2′:3′:3:4)-coumarin, 7-hydroxy-, and 7:8-*di*hydroxy-, and their derivatives, 1673.
2-(2′-Coumaronyl)-Δ²-pyrroline, and its picrate, 188.
***p*-Cresol-3-sulphonic acid**, 2-chloro-5-amino-, 215.
Crotonanilide, *p*-chloro-*o*-nitro-, 1911.
Crotonic acid, esters, 666.
Crotonic acid, γ-bromo-, methyl ester, in synthesis of hydroaromatic ketones, 162.
Crystal-violet, nitration of, 2169.
Culture media, containing nitrates and nitrites, growth of coliform bacteria in, 824, 833, 841, 845.
Curare alkaloids, 265, 1945.
(+)-*cis*- and (−)-*trans*-**Cryptols**, and their derivatives, 996.
(−)-**Cryptone**, cryptols from, 996.
Cyanides. See under Cyanogen.
*neo*Cyanines, preparation and structure of, 690.
Cyanine dyes from 2:3-dihydro-β-quinindene, 1895.
trinuclear, 1872.
Cyanogen :—
Cyanides, parachors and refractivities of, 674.
preparation of amidines from, 303.
Cyanophosphonic acid, diethyl ester, 701.
α-Cyanoprene. See Buta-1:3-diene, 1-cyano-.
β-Cycloylpropionitriles, 186.
2-Cyclylpyrrolidines, formation of, from β-cycloylpropionitriles, 186.
2-Cyclyl-Δ²-pyrrolines, formation of, from β-cycloylpropionitriles, 186.
Cysteine hydrochloride, preparation of, 1339.
Cytidine-2′ phosphate, synthesis of, 1527.

D.

DDT, decomposition of, by basic substances, 1657.
Daphnandra, alkaloids, 2170.
Decahydroquinolines, *cis*- and *trans*-, 1373.
aryl derivatives, 2011.
Decahydrotetra*chano*strychnidine, 1666.
cis-**Decalin**, structure of, 340.
***n*-Decane-1-carboxylic acid**. See Undecoic acid.
***n*-Decoic acid**, *n*-butyl and *n*-propyl esters, 631.
soluble films of, expansion of, at air–water interface, 936.
3-Decoyl-3-methylbutanecarboxylic acid, 1745.
Dec-9-yne-1-carboxylic acid, esters, 677.
Dehydroascorbic acid, and its salts and derivatives, 160.
Dehydro-*l*-ascorbic acid, isolation and properties of, 158.
7-Dehydrocholesterol, preparation of, and its derivatives, 1783.
7-Dehydrocholesteryl bromide and chloride, 1788.
Dehydrodihydrostrychnidine, 1665.
Densitometer–viscometer, 2239.
Desyl dibenzyl phosphate, 1111.
Desyl radical, anionic nature of, compared with cationoid reactivity of the triphenylmethyl radical, 1549.
DL-**Dethiobiotin**, synthesis of, 1552.
Deuterobenzene, spectrum of, absorption, ultra-violet, 483.
α-Deuterobutyric acid, 1088.
α-Deuterohexoic acid, 1088.
Dextran, structure of, from sucrose, 1555.
Diacetimide, preparation of, 1081.
5:5-Diacetylnona-2:7-diene, 1:9-*di*cyano-, 233.
5:5-Diacetylnonane, 1:9-*di*cyano-, 234.
3:4-Dialkylphenols, substitution in, 2143.
Diallyl sulphide, 3:3′-*di*chloro-, 2181.
Diallylamine, *di*-3-chloro-, 2181.
1:1-Di(allyloxy)ethane, 1:1-*di*-3-chloro-, 2182.
Di(allyloxy)methane, *di*-2-chloro-, 2182.
1:1-Di(allylthio)ethane, 1:1-*di*-3-chloro-, 2182.
1:2-Di(allylthio)ethane, 1:2-*di*-3′-chloro-, 2181.
6:6′-Diamidino-2:2′-dimethoxydi-α-naphthylmethane *di*isethionate, 263.
6′:6″-Diamidino-1:5-di-β-naphthoxypentane, salts, 263.
6′:6″-Diamidino-1:3-di-β-naphthoxypropane *di*isethionate, 263.
4′:4″-Diamidino-1:1-diphenyl-2:2-dimethylethylene *di*hydrochloride, 263.
4′:4″-Diamidino-1:1-diphenylethylene, *di*hydrochloride, 262.
4′:4″-Diamidino-1:1-diphenyl-2-methylethylene, *di*benzoate, 262.
4:4′-Diamidinostilbene, preparation of, 308.
Diaminofluorophosphine oxides, 1313.
5:5-Di-*n*-amylhydantoin, 1388.
1:4-3:6-Dianhydromannitol, action of phosphorus tribromide on, 2201.
1:4-3:6-Dianhydrosorbitol, 2:5-*di*acetate, 240.
action of phosphorus tribromide on, 2201.
conversion of, into 1:4-anhydrosorbitol derivatives, 237.
1:4-3:6-Dianhydrosorbitol, 5-*mono*- and 2:5-*di*-chloro-, 2202.
Dianilinofluorophosphine oxide, 1315.
1:4-Dianilinophthalazine, 780.
2:3-Dianilinoquinoxaline, 780.
2:3-Dianilinoquinoxaline, 2:3-*di*-*p*-chloro-, 780.
6-chloro-2:3-*di*-*p*-chloro-, 781.
1:1-Di-*p*-anisyl-2-*p*-ethoxyphenylethylene, 2-chloro-, 155.
Dianisylidenestrychninonic acid, hydrate, 956.
1:1′-Dianthraquinonyl-4:4′-dicarboxylic acid, and its pyridinium salt, 1625.
1:5-Di-α-anthraquinonylimino-2-*tert*.-butylanthraquinone, 1629.
Diarylcyanoarsines, 2208.
NN′-**Diarylformamidines**, synthesis of, 1014.
Diaryl sulphones, *o*-hydroxy-, action of diazomethane on, 605.
1:3-Diaza-acridine, 5-amino-2:4-*di*hydroxy-, and its hydrochloride, 555.
1:3-Diaza-acridine-5-carboxylic acid, 2:4-*di*hydroxy-, and its methyl ester and sodium salt, 554.
Diazo-compounds, aromatic, decomposition of, in aqueous solution, electronic mechanism of, 348.
free-radical reactions of, 882.
replacement of diazo- by nitro-group in, 556.
Diazocyanides, isomeric, Hantzsch's, structure of, 1097.
Diazomethane, and its derivatives, experiments with, 605.
Diazomethyl β-*p*-methylsulphonyl phenylethyl ketone, 1505.
Diazonium groups, replacement of, by nitro-groups, 1512.
Diazonium salts, coupling of, with 3:4-dialkylphenols, 2143.
decomposition of, in neutral solutions, 1512.
Diazosulphonates from β-naphthol-1-sulphonic acid, phthalazine reaction with, 597, 1026, 1249.
anti-**Diazosulphonates** of naphthalene series, isolation of, 1183.
3:3-Di-(5-barbituryl)-1-methyloxindole, 555.
3:3-Di-(5-barbituryl)oxindole, 553.
"Dibenzamidodioxytetrol", structure of, 1958.
Di*meso*benzanthronyl, composition of, from *meso*benzanthrone with alkaline condensing agents, 1622.
6:6′-Di*meso*benzanthronyl, 1625.
action of fused potassium hydroxide on, 1746.
4:6′- and **6:6′-Di*meso*benzanthronylamines**, 1179, 1180.
Dibenzhydryl aminophosphonate, 1110.
phosphite, 1110.

5:6:7:8-Dibenzoalloxazine, 2-imino-, 223.
Dibenzoylmalonic acid, ethyl ester, 556.
Dibenzyl chlorophosphonate, preparation of, and its use in phosphorylation, 1106.
phosphite, preparation and purification of, 1109.
Di(benzylamino)fluorophosphine oxide, 1315.
Dibenzylideneazine, thermal data for, 1190.
Dibenzylidene-ethylenediamine, thermal data for, 1190.
Dibenzylideneglyoxal, structure of, 763.
2:4-3:5-Dibenzylidene sorbitol, 1:6-*di*bromo-, and 1-bromo-6-iodo-, 2203.
1:6-*di*chloro-, 239.
Dibenzylidenestrychninonic acid hydrate, 956.
Dibenzylidene styracitol, 2207.
Di-(3′:5′-benzylidene uridine-2′:2′) phenyl phosphate, 1533.
NN′-**Dibenzyl-*p*-methylsulphonylbenzamidine**, 308.
2:4(5)-Dibenzylthioglyoxaline, and its acetyl derivative, 203.
Di-(*n*-butylamino)fluorophosphine oxide, 1315.
2-γ-Di-*n*-butylaminopropylamino-4-hydroxyquinazoline, hemihydrate, 1770.
2-γ-Di-*n*-butylaminopropylaminoquinazoline, 4-chloro-, sesquipicrate, 1770.
Di*iso*butylene, oxidation of, by chromic acid, 1334.
α-Di*iso*butylene, reaction of, with organic per-acids, 1328.
with selenium dioxide, 1333.
β-Di*iso*butylene, reaction of, with organic per-acids, 284.
with selenium dioxide, 1333.
Di-4-butylformal, *di*-4-chloro-, 809.
NN′-**Dicarbomethoxy-2:2′-*di*aminodiethyl** sulphide, and *NN′-di*nitroso-, 2320.
2:2′-Dicarbomethoxybenzoyl *per*oxide, 2216.
3:3′-Di-(ω-carboxymethylamino)diphenylamine, 1006.
γδ-Dicarboxy-δ-phenyl-*n*-valeric acid, and its trimethyl ester, 978.
Dichromates. See under Chromium.
Dicinnamyl, spectrum of, absorption, 1123.
trans-**Dicinnamyl**, 1116.
iso-**Dicinnamyl**, 1117.
1:4-Dideuterobenzene, spectrum of, absorption, ultra-violet, 461.
Di-2:4-dimethoxyphenyl *di*sulphide, 526.
4:4′-Diethoxybenzophenone, preparation of, 152.
6:7-Diethoxy-1-benzyl-3-methyl*iso*quinoline, 889.
2:2′-Diethoxydiethyl sulphide, 2:2′-*di*-2-chloro-, and its derivatives, 43.
2:2′-*di*-2-hydroxy-, 43.
6:7-Diethoxy-1-3′:4′-dimethoxyphenyl-3-methyl*iso*quinoline, 889.
2:5-Diethoxy-3:6-dimethylpyrazine, 1862.
6:7-Diethoxy-1:3-dimethyl*iso*quinoline, 889.
6:7-Diethoxy-3-methyl*iso*quinolines, synthesis of, 885.
6:7-Diethoxy-1-phenyl-3-methyl*iso*quinoline, and its hydrochloride, 889.
1-3′:4′-Diethoxyphenylpropanol, 2-amino-, and its *N*-acyl derivatives and hydrochloride, 888, 889.
ψ-2-amino-, and its acyl derivatives, and 2-nitro-, acetate, 887, 888.
3:4-Diethoxypropenylbenzene, and its ψ-nitrosite, 887.
ββ-Diethoxypropionylhydrazide, α-amino-, hexoyl derivative, and its benzylidene derivatives, 1967.
***N*-(ββ-Diethoxypropionyl)-D-penicillamine**, *N*-α-amino-, hexoyl derivative, 1967.
3:4-Diethoxypropiophenone, and α-amino-, and its benzoyl derivative, and α-*iso*nitroso-, 888, 890.
3:4-Diethoxypropiophenone azine, 890.
Diethyl amino-, cyano-, and thiocyanato-phosphonates, 701.
2-chloroethyl and 2-fluoroethyl phosphates, 703.
ether. See Ethyl ether.
fluorodithiophosphonate, 1014.
fluorophosphonate, 1012.
di-2-chloro-, and *di*-2-fluoro-, 1013, 1014.
sulphide, 2-hydroxy-, acetyl derivative, 1596.
*di*sulphide, *di*-2-hydroxy-, 46.
2:2′-*di*hydroxy-, and its derivatives, 42.
*tri*sulphide, and 2:2′-*di*chloro-, crystal structure of, 323, 324.
2:2′-*di*iodo-, crystal structure of, 324, 1256.
sulphilimine, 2:2′-*di*bromo-, 37.
Diethylamine, *di*-2-fluoro-, 2176.
ω-Diethylaminoacetanilide, *p*-chloro-*o*-amino- and -*o*-nitro-, 1910.
2-Diethylamino-4-(4-dimethylaminostyryl)-6-methylpyrimidine, 2151.
β-Diethylaminoethoxyamine, and its hydrochloride, 185.
9-β-Diethylaminoethyl*iso*alloxazine, 7-chloro-, and its salts, 1931.
4-β-Diethylaminoethylamino-6:7-benzoquinazoline, 2-chloro-, 1765.
2-β-Diethylaminoethylamino-4-*p*-chlorophenylthioquinazoline, 1771.
4-β-Diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline, 1771.
4-β-Diethylaminoethylamino-6:7-dimethoxyquinazoline, 2-chloro-, 1765.
2-(2-Diethylaminoethylamino)-4-(4-dimethylaminostyryl)-6-methylpyrimidine, 2151.
2-β-Diethylaminoethylamino-4-hydroxyquinazoline, 1769.
4-β-Diethylaminoethylamino-5-, -6-, and **-8-methoxyquinazolines**, 2-chloro-, 1765.
2-β-**Diethylaminoethylamino-6-methylpyrimidine**, 4-amino-, 591.
4-β-Diethylaminoethylamino-7-methylquinazoline, 2-chloro-, 1765.
2-β-Diethylaminoethylamino-4-phenoxy-6-methylpyrimidine, *di*picrate, 590.
2-β-Diethylaminoethylaminoquinazoline, 4-chloro-, and its sesquipicrate, 1770.
4-β-Diethylaminoethylaminoquinazoline, 2:6- and 2:7-*di*chloro-, 2-chloro-6- and -7-nitro-, 1765.
3-β-Diethylaminoethylaminoquinoxaline, 2-amino-, 781.
2-chloro-, and its picrate, 780.
6′-β-Diethylaminoethylamino-4:4′:6-trimethyl-2:2′-dipyrimidylamine, and its dihydriodide, 596.
β-Diethylaminoethylaniline, 5-chloro-2-nitro-, nitro-, and their salts, 1930, 1931.
2-Diethylaminomethylbenziminazole, 5(or 6)-chloro-, 1910.
3-(4-Diethylamino-1-methylbutylamino)anisole, 4-amino-, reaction of, with alloxan, 1719.
4-nitro-, picrate, 1719.
5-(δ-Diethylamino-α-methylbutylamino)-3:4-benzacridine, 8-chloro-, and its picrate, 126.
5-(δ-Diethylamino-α-methylbutyl)amino-7-methoxyacridine, 2-chloro-. See Mepacrine.
2-(δ-Diethylamino-α-methylbutylamino)-4-methoxy-1:3:5-triazine, 6-amino-, and its picrate, 563.
2-δ-Diethylamino-α-methylbutylamino-6-methylpyrimidine, 4-amino-, and its dipicrate, 592.
6-δ-Diethylamino-α-methylbutylamino-2-methylpyrimidine, 4-amino-, *di*picrate, 593.
4-(δ-Diethylamino-α-methylbutylamino)-1:3:5-triazine, 2-chloro-6-amino-, 563.
9-(γ-Diethylaminopropyl)*iso*alloxazine, 7-chloro-, and its salts, 1931.
5-(γ-Diethylaminopropylamino)-1:2-benzacridine, 8-chloro-, 125.
2- and **4-γ-Diethylaminopropylamino-4-** and **-2-*p*-chlorophenylthioquinazolines**, 1771.
2-γ-Diethylaminopropylamino-4-hydroxyquinazoline, and its hydrate, 1770.
4-γ-Diethylaminopropylamino-6-methylpyrimidine, 2-amino-, 585.
4-γ-Diethylaminopropylamino-2-*p*-methylsulphonylphenyl-6-methylpyrimidine *di*hydrochloride, 1507.
5-(γ-Diethylaminopropylamino)-1:2:3′:2′-pyridoacridine, 8-chloro-, 126.
5-(γ-Diethylaminopropylamino)-3:4:3′:2′-pyridoacridine, 8-chloro-, 126.
2-γ-Diethylaminopropylaminoquinazoline, 4-chloro-, 1770.
3-γ-Diethylaminopropylaminoquinoxaline, 2-amino-, 781.
2-chloro-, and its salts, 780.
4-γ-Diethylaminopropylamino-2-*p*-tolylthioquinazoline, 1771.
(γ-Diethylaminopropyl)aniline, 5-chloro-2-nitro-, and its salts, 1931.
Diethylcarbamic acid, methyl ester, 878.
Diethylcarbamyl fluoride, 2186.
1:1′-Diethyl-2:4′-carbocyanine iodide, 689.
Diethylcyanamide, *di*-2-chloro-, 2174.
Diethyldicyandiamide, 1633.
Diethyl-2-fluoroethylamine, *di*-2-chloro-, 2177.
N-(*NN*-**Diethylguanyl**)-*S*-**methyl*iso*thiourea** hydriodide, 1654.
NN-**Diethylguanylthiourea**, 1654.
meso-**αβ-Diethylidenedibenzyl**, 1122.

1:3-2:4-Diethylidene D-sorbitol, 5:6-diacetyl derivative, 1936.
Diethyl ketoxime, benzenesulphonate, 1518.
Diethylnitrosoamine, preparation and physical properties of, 1846.
3:3-Diethyloxaselenacarbocyanine iodide, 689.
3:3′-Diethyloxathiacarbocyanine iodide, 690.
NN′-**Diethylpiperazine**, *NN′-di*-2-chloro-, and its dihydrochloride, 2175.
3:6-Diethylpyrazine, 2-amino-, and its derivatives, and 2-hydroxy-, 1858.
2:5-*di*cyano-, and 2-hydroxy-, 1863.
3:6-Diethylpyrazine-5-carboxylic acid, 2-hydroxy-, 1863.
Diethyl sulphone, 2-chloro-, 2179.
2:2′-Diethylsulphonyldiethyl sulphone, 2:2′-*di*-2-chloro-, 41.
2:2′-Di(ethylthio)diethyl ether, 2:2′-*di*-2-bromo-, 2:2′-*di*-2-cyano-, 2:2′-*di*-2-hydroxy-, 2:2′-*di*-2-iodo-, and 2:2′-*di*-2-thiocyanato-, and their derivatives, 36, 37.
2:2′-*di*-2-chloro-, and its derivatives, 35.
sulphide, 2:2′-*di*-2-bromo-, 42.
2:2′-*di*-2-chloro-, and its derivatives, and 2:2′-*di*-2-iodo-, and 2:2′-*di*-2-thiocyanato-, 40, 41.
*di*sulphide, 2:2′-*di*-2-hydroxy-, 41.
sulphoxide, 2:2′-*di*-2-chloro-, and 2:2′-*di*-2-hydroxy-, 41.
2:2-Di(ethylthio)diethyl sulphone, 2:2′-*di*-2-chloro-, and 2:2′-*di*-2-hydroxy-, 41.
2:3-Di(ethylthio)-1:4-dioxan, 2:3-*di*-2-chloro-, and 2:3-*di*-2-hydroxy-, 41.
2:2′-Di(ethylthio)di-*n*-propyl sulphide, 2:2′-*di*-2-chloro-, and 2:2′-*di*-2-hydroxy-, 41.
1:2-Di(ethylthio)ethane, 1:2-*di*-2-chloro-, 44.
α-(ββ-Diethylthiopropionamido)-β-methoxy*iso*valeric acid, α-amino-, hexoyl derivative, 1968.
ββ-Diethylthiopropionic acid, α-amino-, hexoyl derivative, ethyl ester and hydrazide, 1967.
N-(**ββ-Diethylthiopropionyl**)**glycine**, *N*-α-amino-, hexoyl derivative, 1967.
Diguanides, formation of, from guanylthioureas, 1645.
5:5-Di-*n*-heptylhydantoin, 1388.
Di*cyclo*hexyl fluorophosphonate, 1013.
Di(*cyclo*hexylamino)fluorophosphine oxide, 1315.
Di*cyclo*hexylcarbamic acid, ethyl ester, 878.
2:3-Dihydroacenaphthyleno(7′:8′:2:3)indole-1-carboxylic acid, 3-nitro-2-hydroxy-, 2-acetyl derivative, esters, 1248.
5:10-Dihydroarsacridine, 10-chloro-, and 10-cyano-, 295.
3:10-*di*chloro-, and 3-chloro-10-cyano-, 298.
3:4-Dihydro-1:2-benzanthracene, 3:4-*di*hydroxy-, and its diacetate, 172.
2:3-Dihydrobenzfuran, 4-hydroxy-, 894.
1:2-Dihydro-3:4-benzpyrene, 1:2-*di*hydroxy-, and its diacetate, 173.
Dihydrobetulonic acid, and its derivatives, 950.
1:2-Dihydrochrysene, 1:2-*di*hydroxy-, and its diacetate, 173.
Dihydro-1:2:5:6-dibenzanthracene, *di*hydroxy-, and its diacetate, 172.
Dihydroevodione, and its derivatives, 2007.
Dihydromyrcene, spectrum of, infra-red absorption, and structure, 1415.
2:3-Dihydropsoralene, synthesis of, 2254.
1:2-Dihydropyrene, 1:2-*di*hydroxy-, and its diacetate, 173.
2:3-Dihydro-β-quinindene, cyanine dyes from, 1895.
ethiodide, 1897.
methiodide 3-*p*-dimethylaminoanil, 1897.
Dihydrostrychnine, *x*-hydroxy-, 955.
Dihydro-β-strychnine, experiments with, 951.
methyl ether, 954.
Dihydro*neo*strychninephosphorous acid, 956.
Dihydrothionaphthen sulphone, iodo-, 1617.
Dihydro*iso*visnagin, 2264.
Dihydrovisnagone, and its 2:4-dinitrophenylhydrazone, 2264.
Diketen, structure of, from conductivity and potential measurements, 1323.
1:3-Diketo-2-acetonylindane, 979.
2:4-Diketo-1-acetylpyrrolidine, 3-amino-, 3-acetyl derivative, 1959.
2:5-Diketo-3-(4′-amino-2′:5′-dimethoxyphenyl)*iso*indolinopyrazolidocoline, and its acetyl derivatives, 284.
6:17-Diketoandrostane, derivatives of, 1043.
1:4-Diketo-3-(2′:4′:6′-*tri*bromophenyl)tetrahydrophthalazine, 599.
7:12-Diketo-3-carbethoxymethylcholanic acid, 3-hydroxy-, ethyl ester, 1361.
7:12-Diketo-3-carboxymethylenecholanic acid, and its diethyl ester, 1361.
1:4-Diketo-3-(2′-chloro-5′-nitrophenyl)tetrahydrophthalazine, 208.
1:4-Diketo-3-(2′-chlorophenyl)tetrahydrophthalazine, 1029.
1:4-Diketo-3-(3′-chlorophenyl)tetrahydrophthalazine, 600.
6:7-Diketocholestane, 3(β)-hydroxy-, 1042.
7:12-Diketo-3-cyanocarbethoxymethylenecholanic acid, ethyl ester, 1360.
2:4-Diketo-1:3-dimethyl-1:2:3:4-tetrahydro-1:3-diaza-acridine-5-carboxylic acid, methyl ester, 554.
2:3-Diketo-1:4-dimethyl-1:2:3:4-tetrahydroquinoxaline, 521.
1:3-Diketoindane, 2-hydroxy-, 2-acetyl and 2-benzoyl derivatives, 51.
Diketolanostane, 990.
Diketolanostanol, 990.
Diketolanostanyl acetate, 989.
Diketolanostene, 990.
2:4-Diketo-10-methyl-2:3:4:10-tetrahydro-1:3-diaza-acridine-5-carboxylic acid, and its methyl ester, 555.
2:5-Diketo-3-(4′-nitro-2′:5′-dimethoxyphenyl)*iso*indolinopyrazolidocoline, 284.
6:7-Dimethoxyalloxazine, 1930.
2:6-Dimethoxy-3-allylacetophenone, 4-hydroxy-, and its acetate, 2264.
2-(2′:5′-Dimethoxyanilino)*iso*indolinone-3-acetic acid, 2-4′-nitro-, and its methyl ester, 283.
5:4′-Dimethoxy-3-anisoylflavone, 8-hydroxy-, 8-anisyl derivative, 2142.
2:5-Dimethoxybenzenesulphonic acid, 4-chloro-, and its derivatives, 215.
3′:7-Dimethoxy-3:4-benzfluorenone-1-carboxylic acid, methyl ester, 1269.
γ-(Dimethoxybenzoyl)butyric acid, γ-hydroxy-, 1050.
4:5-Dimethoxybenzylideneacetone, 2-nitro-, 1246.
Di-*o*- and -*p*-methoxybenzylidenesuccinic acids, and their anhydrides, 1271.
1:4-Dimethoxy-3-(2′-chlorophenyl)-3:4-dihydrophthalazine, 1027.
4:10-Dimethoxychrysene, 2:8-*di*hydroxy-, 2:8-diacetyl derivative, 1001.
3:4-Dimethoxycinnamic acid, 2-nitro-α-amino-, α-acetyl derivative, azlactone, 378.
5:7-Dimethoxycoumarin, 4-hydroxy-, and its acetate, 174.
2:2′-Dimethoxydi-α-naphthylmethane, 6:6′-*di*bromo- and -*di*cyano-, 263.
5:4′-Dimethoxyflavone, 8-hydroxy-, and its 8-anisyl derivative, 2142.
trans-**5:14-Dimethoxy-1:2:9:10:11:18-hexahydrochrysene**, 1001.
5:6-Dimethoxyindole, 2225.
5:7-Dimethoxy-3-methylcoumarin, 4-hydroxy-, and its acetate, 175.
1:5-Dimethoxynaphthalene, 2:6-*di*bromo-, preparation of, 1284.
meso-**ββ′-Di-*p*-methoxyphenyladipic acid**, *meso*-**ββ′-*di*hydroxy-**, 1001.
4:7-Dimethoxy-3-phenylcoumarin, 175.
7:4′-Dimethoxy-3-phenylcoumarin, 4-hydroxy-, and its derivatives, 175.
trans-**ββ′-Di-*p*-methoxyphenyl-*aa′*-dihydromuconic acid**, 1001.
4′:7-Dimethoxy-1-phenyl-3:4-dihydronaphthalene, 1269.
3-(2′:5′-Dimethoxyphenyl)-3:4-dihydrophthalazine-4-acetic acid, 1-hydroxy-3-4′-amino-, 282.
1-hydroxy-3-4′-nitro-, and its derivatives, 282.
3-(2′:5′-Dimethoxyphenyl)-3:4-dihydrophthalazine-1-sulphonic-4-acetic acid, sodium hydrogen salt, 282.
2′:5′-Dimethoxy-3-phenyl-1-methylphthalaz-4-one, 4′-nitro-, 283.
2′:5′-Dimethoxy-3-phenyl-4-methylphthalaz-1-one, 4′-amino-, and 4′-nitro-, and its picrate, 283.
2′:5′-Dimethoxy-*N*-phenyl-3-methylphthalimidine, 4-amino-, 283.
4′:7-Dimethoxy-1-phenylnaphthalene, 1269.
2′:5- and 4′:7-Dimethoxy-1-phenylnaphthalene-2:3-dicarboxylic acids, synthesis of, and their derivatives, 1270.
2(3′:4′-Dimethoxyphenyl)pyrrolidine, and its picrate, 187.
2(3′:4′-Dimethoxyphenyl)-Δ²-pyrroline, and its picrate, 187.
4-3′:4′-Dimethoxyphenylsulphonylbenzoic acid, 603.
2:4-Dimethoxyphenyl 2-thienyl sulphone, 526.

3:4-Dimethoxyphenyl *p*-tolyl sulphone, 602.
δ-(Dimethoxyphenyl)valeric acid, δ-hydroxy-, 1051.
4:5-Dimethoxy-1:2:2′:3′-pyridoacridine, 291.
6:7-Dimethoxyquinazoline, 2:4-*di*chloro-, and 2:4-*di*hydroxy-, 1764, 1765.
3:9-Dimethoxyquinindoline, and its 6-acetyl derivative, 923.
5:6-Dimethoxy-1-α-quinolylbenztriazole, 923.
2:3-Dimethoxyquinoxaline, preparation of, 521.
Dimethyl ether. See Methyl ether.
sulphide, evolution of, by marine algæ, 1591.
2-Dimethylaminoacridine, 1227.
3-Dimethylaminoacridine, 7-amino-, 1227.
7-Dimethylaminoalloxazine, and its sodium derivative, 1929,
p-Dimethylaminobenzaldehyde, condensation of, with 4-methylpyrimidine derivatives, 1715.
p-Dimethylaminobenz-o-toluidide, and its picrate, 1604.
3-*p*-Dimethylaminobenzylidene-2:3-dihydro-β-quinindene ethiodide, 1898.
7-Dimethylaminobenzylidene-2:4-diphenyldihydropyrindene methiodide, 1898.
4-Dimethylaminobutylbenzyl cyanide, 809.
***p*-Dimethylaminocinnamic acid**, α-amino-, α-benzoyl derivative, 88.
7-Dimethylamino-9-β-diethylaminoethyl*iso*alloxazine, and its salts, 1929.
3-Dimethylamino-β-diethylaminoethylaniline, and its picrates, 1928.
5-Dimethylamino-β-diethylaminoethylaniline, 2-nitro-, and its picrate, 1929.
3-Dimethylaminodiphenylamine, and its *N*-acetyl derivative, 1229.
3′-Dimethylaminodiphenylamine, 4-amino-, and 4-nitro-, 1230.
3′-Dimethylaminodiphenylamine-2-sulphonic acid, 4-nitro-, hemihydrate, 1229.
7-Dimethylamino-9-methyl*iso*alloxazine, 1929.
β-*p*-Dimethylaminophenylalanine, 88.
γ-Dimethylamino-α-phenylbutyric acid, ethyl ester, 809.
4-[2-(4-Dimethylaminophenyl)ethyl]-6-methylpyrimidine, 2-chloro-, 2151.
2-*p*-Dimethylaminophenylguanidino-6-methylpyrimidine, 4-hydroxy-, 579.
ε-Dimethylamino-α-phenylhexoic acid, ethyl ester, 809.
2-(4-Dimethylaminostyryl)benzoxazole, 2153.
4-(4-Dimethylaminostyryl)-6-methylpyrimidine, 2-amino-, 2-acetyl derivative, 2151.
2-chloro-, 2150.
2-(4-Dimethylaminostyryl)-β-naphthathiazole, 2153.
1-(4-Dimethylaminostyryl)phthalazine, 2153.
4-(4-Dimethylaminostyryl)pyrimidine, and its picrate, 2150.
4-(*p*-Dimethylaminostyryl)pyrimidine, 6-chloro-, 2:6-*di*chloro-, and 6-hydroxy-, 1715.
2-(4-Dimethylaminostyryl)quinoline, 6-amino-, and 6-nitro-, 2152.
2-(4-Dimethylaminostyryl)thiazole, 2153.
4-(*p*-Dimethylaminostyryl)uracil, 1715.
4-*p*-Dimethylaminostyryluracil, 5-nitro-, 1135.
Dimethylaminosulphonyl chloride and fluoride, 1316.
3-Dimethylamino-*p*-toluenesulphonanilide, 1928.
6′-Dimethylamino-4:4′:6-trimethyl-2:2′-dipyrimidylamine, and its hydrobromide, 596.
Dimethyl-*n*-amylsulphonium iodide, 1596.
Dimethylaniline, derivatives, nitration of, 2169.
Di-(*N*-methylanilino)fluorophosphine oxide, 1315.
2:3-Dimethyl-5-azaquinoxaline, and 7-bromo-, 1391.
6:8-Dimethyl-3:4-benzfluorenone, 1232.
2:3-Dimethyl-1:3-butadiene, condensation of, with *p*-benzoquinone, 1499.
Dimethyl-2-carboxyethylsulphonium chloride, 1596.
hydroxide, and its salts, 1591.
2:2-Dimethylchroman-4-one, 7:8-*di*hydroxy-, 1612.
2:3-Dimethylcinchoninic acid, 6-bromo-, and its picrate, and 6:8-*di*chloro-, 108.
3:5-Dimethylcoumaran, 6-hydroxy-, and its 6-benzyl derivative and *p*-nitrobenzoate, 2259.
3:6-Dimethylcoumarone-2-acetic acid, 2260.
3:6-Dimethylcoumarone-2-carboxylic acid, 2260.
Dimethyldi-(2-chloroethyl)ammonium chloride, 2176.
Dimethyldicyandiamide, 1633.
N^1:N^3-Dimethyldicyandiamide, 1650.
Dimethyldi-(2-fluoroethyl)ammonium iodide, 2176.
9:10-Dimethyldihydro-1:2-benzanthracene, *di*hydroxy-, and its diacetate, 172.
2:5-Dimethyl-2:5-di*neo*pentyl-1:4-dioxan, 1329.
4:3′-Dimethyldiphenyl sulphide, 2:6′-*di*nitro-, 2020.
4:4′-Dimethyl-2:2′-dipyrimidylamine, 6:6′-*di*chloro-, and 6:6′-*di*hydroxy-, 596.
2:4-3:5-Dimethylene mannitol, 1:6-*di*bromo-, 2203.
3:6′-Dimethyl-1′-ethylthiaquino-2:2′-carbocyanine iodide, 690.
3:4-Dimethyl-4-ethylthiazolidine-2-thione, 5-imino-, 1621.
3:4-Dimethyl-4-ethylthiazolid-5-one-2-thione, 1621.
2:4-Dimethylfluoranthene, synthesis of, and its derivatives, 1137.
6-(2:3-Dimethyl-*d*-glucuronosido) 2:4-dimethyl-*d*-galactoside, methyl ester, 123.
Dimethylglyoxime, complex compounds of, with metals, 378.
Dimethylglyoximepalladium, metallic salts of, 380.
1:3-Dimethyl*cyclo*hexa-3:6-diene-5-one, 2:2:4:6-*tetra*chloro-, 2-chloro-2:4:6-*tri*bromo-, and 2:2:4-*tri*chloro-6-bromo-, 369, 370.
5:6-Dimethyl-3-*spirocyclo*hexyldihydrophthalide, 807.
4:4-Dimethyl-2-hydroxymethylpent-1-ene 3:5-*di*nitrobenzoate, 1330.
Dimethyl D-mannonic acid, phenylhydrazide, 1279.
***NN*-Dimethyl-*p*-methylsulphonylbenzamidine**, preparation of, 307.
Dimethyl-2-(2:4:6-*tri*nitrophenyl)ethylsulphonium iodide, 1615.
3:3-Dimethylnonanecarboxylic acid, and its *S*-benzylthiouronium salt, 1745.
3:3′-Dimethyloxathiacarbocyanine iodide, 690.
2:2-Dimethyloxazolidine, 5-imino-, 205.
2:3-Dimethylpentane, *hexadeca*fluoro-, spectrum of, infra-red absorption, 1432.
3:3-Dimethylpentanecarboxylic acid, and its *S*-benzylthiouronium salt, 1745.
2:2-Dimethylpentan-4-ol 3:5-*di*nitrobenzoate, 1329.
1:3-Dimethylphenanthridine, 9-amino-, 1540.
9:10-Dimethylphenanthridinium bromide, 2-amino-, 192.
6-amino-, 194.
N^1-4-3′:5′-Dimethylphenoxyphenyl-N^5-*iso*propyldiguanide hydrochloride, 1635.
***O*-Dimethylpiscidic acid**, and its derivatives, 259.
Dimethyl purpurogallin, 1049.
3:6-Dimethylpyrazine, 2-amino-, and its 2-propionyl derivative, 1858.
2-amino-5-hydroxy-, 2-chloro-, 4-oxide, 2:5-*di*chloro-, 2-chloro-5-hydroxy-, and 2-hydroxy-, 4-oxide, 1861, 1862.
2:5-*di*cyano-, 1864.
2:6-Dimethyl-3-pyridazone, chlorination of, 2191.
2:6-Dimethyl-3-pyridazone, 5-*mono*-, and 4:5-*di*-chloro-, 2193.
2:6-Dimethyl-3-pyridazone-4-carboxylic acid, 2194.
2:6-Dimethyl-3-pyridazone-5-carboxylic acid, 2193.
5:11-Dimethyl*iso*quinindoline, 924.
5:11-Dimethylquinindolinium iodide and methochloride, 924.
2:3-Dimethylquinoline, 6-bromo-, 108.
[2-(1:6-Dimethylquinoline)][3-(4-methyldihydro-β-quinindene)]-dimethincyanine iodide, 1897.
3:5-Dimethyl D-ribose phenylosazone, 2036.
6:7-Dimethyltetrahydro-α-naphthaquinone, and its dioxime, 1500.
1:3-Dimethyl-5:6:7:8-tetrahydrophenanthridine, 9-amino-, 1540.
3:3′-Dimethylthiathiazolinocarbocyanine iodide, 690.
***N′S*-Dimethyl*iso*thiourea**, *N*-cyano-, 1633.
3:3-Dimethyltridecanecarboxylic acid, and its *S*-benzylthiouronium salt, 1745.
Dimorpholinofluorophosphine oxide, 1315.
1:5-Di-α-naphthoxypentane, 4′:4″-*di*bromo-, 2′:2″:4′:4″-*tetra*bromo-, and 4′:4″-*di*cyano-, 263.
1:5-Di-β-naphthoxypentane, 6′:6″-*di*bromo- and -*di*cyano-, 263.
1:3-Di-β-naphthoxypropane, 6′:6″-*di*bromo- and -*di*cyano-, 263.
2:2′-Dinaphthyl, 4:4′-*di*amino-, and 4:4′-*di*hydroxy-, preparation of, and their derivatives, 1714.
1:1′-Dinaphthyl sulphide, 2:4:4′-*tri*nitro-, 2022.
αβ-Di-(2-naphthyl)acrylic acid, 1603.
Di-2-naphthylchloroarsine, 2210.
Di-2-naphthylcyanoarsine, 2212.
1:2-Di-(1- and -2-naphthyl)ethylenes, 1602.
Dioxan, equilibrium of, with hydrogen chloride and water, 1460.
6:12-Dioxa-3:9:15-trithiaheptadecane, 1:17-*di*chloro-, 43.
Diphenacyl-*p*-ethylaniline, 869.

Diphenacyl-*p*-toluidine, 869.
Diphenyl, 2-nitro-3′-amino-, 194.
2-nitro-4-amino-, and 2-nitro-4:4′-*di*amino-, 4′-acetyl derivative, 192.
*s-di*nitro-derivatives, preparation of, 264.
Diphenyl fluorophosphonate, 1014.
sulphide, 2′-chloro-4:4′-*di*nitro-2-amino-, and 2:2′-*di*chloro-4:4′-*di*nitro-, preparation and derivatives of, 1104.
4:4′-*di*nitro-2:2′-*di*amino-, preparation of, 873.
*di*sulphide, crystal structure of, 323.
mono- and *di*-sulphides, 2:2′:4:4′-*tetra*nitro-, reductions of, 1002.
sulphoxide, 2:2′-*di*chloro-4:4′-*di*nitro-, 1105.
2:2′:4:4′-*tetra*nitro-, 1003.
***NN*-Diphenylacetamidine**, preparation of, 1522.
***NN′*-Diphenylacetamidine**, preparation of, 1618.
1:1-Diphenyl-2-*p*-acetamidophenylethylene, 1080.
1:1-Diphenyl-2-*p*-acetylphenylethylene, 1080.
DL-ββ′-Diphenyladipic acid, 1000.
***meso*-ββ′-Diphenyladipic acid**, 1001.
6:9-Diphenyl*iso*alloxazine, 222.
Diphenylamine, 3-amino-, and its acyl derivatives, 1228.
3:4′-*di*amino-, 1229.
3:3′-*di*amino- and 3:3′-*di*nitro-, preparation of, and their derivatives, 1004.
Diphenylamine-2-aldehyde, 1230.
Diphenylamine-2-carboxyanilide, 5-nitro-, 1230.
Diphenylamine-2-carboxyhydrazide, and 5-amino-, 1230.
Diphenylamine-6-carboxyhydrazide, 3-nitro-, 1230.
Diphenylamine-2-carboxy-(β-*p*-toluenesulphon)hydrazide, and 5-nitro-, 1230.
Diphenylamine-2:5-dicarboxylic acid, 34.
Diphenylarsonous acid, 2-amino-, 2-acetyl derivative, 2209.
2-chloro-, 2209.
2:3-Diphenyl-5-azaquinoxaline, 6-amino-, and its acetyl derivative, and 7-bromo-, and its trimethiodide, 1391.
1:1′-Diphenylazopropane, 686.
***s*-1:1′-Diphenylazopropane**, *s-di*-1:1′-*p*-amino-, 1:1′-*p*-diacetyl derivative, 685.
***NN′*-Diphenylbenzamidine**, preparation of, 1618.
1:3-Diphenylbenz*iso*furan, polymerisation of, 2129.
Diphenylbutadiene, thermal data for, 1190.
1:1-Diphenylbut-2-ene, 1-cyano-, 1994.
1:2-Diphenyl-1-*p*-chlorophenylethylene, and 1-bromo-, and nitro-, 1080, 1081.
Diphenylcarboxylic acids, 3-nitro-, 2219.
Diphenyl-2-carboxylic acid, 4-nitro-, methyl ester, 2218.
Diphenylchloroarsine, 2-amino-, 2-acetyl derivative, 2-chloro-, and *di*-*o*-chloro-, 2210.
Diphenylchloroarsinecarboxylic acids, and their methyl esters, 2210.
Di-5-phenyl-5-cyanoamylformal, 809.
Diphenylcyanoarsines, amino-, and *di*amino-, chloro-, and *di*chloro-, 2211, 2212.
Diphenylcyanoarsinecarboxylic acids, methyl esters, 2212.
1:10-Diphenyldeca-1:9-diene, spectrum of, absorption, 1124.
***NN*-Diphenyldicyandiamide**, 1634.
***N*¹:*N*⁵-Diphenyldiguanide**, *N*¹:*N*⁵-*di*-*p*-chloro-, 1644.
ββ′-Diphenyl-αα′-dihydromuconic acid, 1000.
9:10-Diphenyldihydrophenanthrene, 9:10-*di*hydroxy-, complexes of, with pyridinium salts, 385.
1:1-Diphenyl-2:2-dimethylethylene, 4′:4″-*di*bromo- and -*di*cyano-, 262, 263.
Diphenyl disulphone, crystal structure of, 324.
2:2-Diphenylethane, 1:1:1-*tri*chloro-2:2-*di*-*p*-amino-, 1458.
1:1:1-*tri*chloro-2:2-*di*-4-chloro-, decomposition of, by basic substances, 1657.
1:2-Diphenyl-1-*p*-ethoxyphenylethylene, 2-bromo-, 155.
***N*¹:*N*⁵-Diphenyl-*N*³-ethyldiguanide**, *N*¹:*N*⁵-*di*-*p*-chloro-, and its hydrochloride, 1641.
1:1-Diphenylethylene, diamidino-derivatives from, 261.
1:1-Diphenylethylene, 4′:4″-*di*bromo- and -*di*cyano-, 262.
2:2-Diphenylethylene, 1:1-*di*chloro-2:2-*di*-*p*-amino-, and its dibenzoyl derivative, and 1:1-*di*chloride-2:2-*di*-*p*-nitro-, 1459.
***NN′*-Diphenylformamidine**, preparation of, 1618.
***NN′*-Diphenylformamidine**, *di*-*o*- and -*m*-chloro-, hydrochlorides, 1015.
***N*:*N′*-Diphenylguanylthiourea**, *N*:*N′*-*di*-*p*-chloro-, 1643.
1:4-Diphenylhexa-1:5-diene, 1116.
spectrum of, absorption, 1124.
3:4-Diphenylhexa-1:5-diene, 1116.
3:4-Diphenyl-*n*-hexane, derivatives, synthesis of, 684.
3:4-Diphenyl-*n*-hexane, *pp′-di*amino-, and its derivatives, 685. *pp′-di*bromo-, *pp′-di*hydroxy-, *pp′-di*nitro-, and *tri*nitro-, 686.
Diphenylmethane, oxidation of, by chromic acid, 1670.
Diphenylmethane, 5-chloro-2-amino-, and its derivatives, 297. 5-nitro-2-amino-, and its 2-acetyl derivative, 298, 299.
Diphenylmethane-2-arsonic acid, 5-chloro-, 298.
***N*¹:*N*⁵-Diphenyl-*N*³-methyldiguanide**, *N*¹:*N*⁵-*di*-*p*-chloro-, and its hydrochloride, 1641.
1:1-Diphenyl-2-methylethylene, 4′:4″-*di*bromo- and -*di*cyano-, 262.
3:3-Diphenyl-5-methyl-2-ethylidenetetrahydrofuran, 1994.
3:3-Diphenyl-5-methyl-2-ethyltetrahydrofuran, 2-hydroxy-, and its 2-acetyl derivative, 1994.
3:3-Diphenyl-5-methyltetrahydrofuran, 2-imino-, and its 2-acetyl derivative, 1994.
1:1-Diphenyl-2-*p*-nitrophenylethylene, 1081.
2:2-Diphenyl-1-*p*-nitrophenylethylene, 1-bromo-, 1081.
2:2-Diphenylpent-4-en-1-carboxyamide, 1994.
1:1-Diphenyl-2-*p*-propionamidophenylethylene, 1080.
1:1-Diphenyl-2-*p*-propionylphenylethylene, 1080.
Di-3-phenylpropylformal, *di*-3-cyano-, 808.
3:6-Diphenylpyrazine, 2-amino-, and its derivatives, 1858, 1859.
Diphenyl *di*sulphide-*pp′*-bis(*di*chloro)arsine, 375.
Diphenyl *di*sulphide-*pp′*-diarsonic acid, 375.
Diphenyl sulphone, 2:2′-*di*chloro-4:4′-*di*nitro-, 1105.
p-cyano-, 382.
Diphenyl-4′-sulphonic acid, 3-amino- and 3-nitro-4-hydroxy-, and 4-hydroxy-, and its sodium salt, 216.
***CN*-Diphenylsydnone**, 2309.
αγ-Diphenyltetronic acid, 49.
1:1-Diphenyl-2-*p*-*n*-valerylphenylethylene, 1080.
2-*p*-Diphenylylguanidino-6-methylpyrimidine, 4-hydroxy-, 579.
***N*¹-*p*-Diphenylyl-*N*⁵-*iso*propyldiguanide**, 1635.
Dipiperidinoanthanthrone, 1181.
Dipiperidinofluorophosphine oxide, 1315.
2:6-Dipiperidino-4-methylpyrimidine, 2151.
2:6-Dipiperidino-4-*p*-nitrostyrylpyrimidine, 5-nitro-, 1134.
2:6-Dipiperidino-4-styrylpyrimidine, 5-nitro-, 1132.
Dipole moments of *C*- and *N*-substituted sydnones, 2269.
Di-*p-n*-propoxyphenyl-*p*-ethoxybenzylcarbinol, 155.
Dipropyl fluorophosphonates, 1012.
Di-*n*-propyl sulphide, 2:2′-*di*chloro-, and 2:2′-*di*hydroxy-, 39.
Di*iso*propyl fluorophosphonate, 695.
6:6′-Di*iso*propylamino-4:4′-dimethyl-2:2′-dipyrimidylamine, 597.
Di-*n*-propylcyanogold, structure of, 64.
***N*¹:*N*³-Di*iso*propyldicyandiamide**, 1650.
2:2-Di-*n*-propyldiethyl sulphide, 2:2′-*di*-2-chloro-, and 2:2′-*di*-2-hydroxy-, 41.
Di*iso*propylideneglyoxal, structure of, 763.
2:2′-Di-(2-propylthio)diethyl ether, 2:2′-*di*-2-chloro-, and 2:2′-*di*-2-hydroxy-, 41.
2:2′-Di-(*n*-propylthio)di-*n*-propyl sulphide, 2:2′-*di*-2-chloro-, and 2:2′-*di*-2-hydroxy-, 41.
2:2′-Di-(*n*-propylthio)di*iso*propyl ether, 42.
1:2-Di-(*n*-propylthio)ethane, 1:2-*di*-2-chloro-, and 1:2-*di*-2-hydroxy-, 46.
2:6′-Diquinolyl, 2010.
2:6′-Diquinolyl-4-carboxylic acid, 2010.
Disalicylides, stereochemistry of, 891.
Dissociation, electrolytic. See under Electrolytic.
Distillation apparatus, 2289.
4:6-Distyrylpyrimidine, 2-chloro-, 2151.
Diterpenes, 1888.
2:2′-Dithienyl *di*sulphide, preparation of, 770.
Di-2-thienylcyanoarsine, 2212.
2:4-Dithio-5-ω-carbethoxy-*n*-butylhydantoin, 2033.
***N*-Dithiocarbobenzyloxyaminomalonic acid**, ethyl ester, 1059.
***N*-Dithiocarbobenzyloxy-ββ-diethoxyalanine**, and its methyl ester, 1059.
***N*-Dithiocarbobenzyloxyglycine**, and its benzylamide, 1058.
***N*-Dithiocarbocarbethoxyglycine**, 1060.
2:4-Dithio-5-1′-ethyl-*n*-amylhydantoin, 2032.
2:4-Dithio-5-*n*-hexylhydantoin, and its monoacetyl derivative, 2032.

2:4-Dithiohydantoin, and its 1:3-diacetyl and 5-*iso*propylidene derivatives, 206.
4:8-Di-*p*-toluidino-2-*tert.*-butylanthraquinone, 6-bromo-1:5-*di*amino-, 1629.
Di-*p*-tolyl *di*sulphide, crystal structure of, 323.
Ditolylarsonous acids, 2209.
Ditolylcyanoarsines, 2211.
Di-*p*-tolyl disulphone, crystal structure of, 325.
***NN'*-Ditolylformamidines**, hydrochlorides, 1015.
Di-*p*-toluylidenesuccinic acid, and its anhydride, 1271.
Diuridine-2':2' phosphate, synthesis of, 1532.
***meso*-αβ-Divinyldibenzyl**, 1111.
***meso*-αβ-Divinyldibenzyl series**, isomorphism and molecular configuration in, 1118.
***n*-Dodecoic acid**, *n*-butyl and *n*-propyl esters, 631.
Dyes, acid, blue, from amino- and nitro-butylanthraquinones, 1627.

E.

Egg-plum gum, structure of, 120.
Electrical conductivity of oxides and spinels at high temperatures, 1729.
Electrodes, antimony, behaviour of, in air, 752.
out of contact with air, 756.
copper, potential of, 740.
in copper sulphate solution, 749.
metallic, 740, 749, 752, 756, 759.
Electrolytic dissociation, 1051.
Electronegativity of bonded groups, 399.
Electrostatic energy. See under Energy.
Elements, periodic system of, new, 318.
radioactive. See under Radioactive.
Elimination reactions, mechanism of, 2038, 2043, 2049, 2055, 2058, 2065, 2072, 2077, 2084, 2090, 2093.
Energy, binding, in hydrocarbons, 1448.
bond and dissociation, 398.
electrostatic, differences, application of the method of, 1197.
1:2-Epoxy-2:4:4-trimethylpentane, 1329.
2:3-Epoxy-2:4:4-trimethylpentane, 286.
Epoxy-2:4:4-trimethylpentanes, reaction of, with sulphuric acid, 1332, 1333.
1:2-Epoxy-2:4:4-trimethylpentan-3-ol, 287.
Ergosta-8(9):14-dien-3(β)-yl benzoate, 793.
Ergostan-3(β)-yl benzoate, 1356.
Ergost-7-en-3-one, 793.
Esters, aliphatic, carboxylic, parachors and refractivities of, 624.
preparation of, 628.
containing phosphorus, 695, 699. 1010, 1313.
reaction of, with amines, 1989.
Ethane, 1:1:1-*tri*chloro-2:2-*di*amino-, 2:2-dibenzoyl and -di-*p*-toluoyl derivatives, 2322.
*di*chloro*tetra*fluoro-, and iodo*penta*fluoro-, 2190.
1:1:1-*tri*fluoro-, spectrum of, infra-red absorption, 1428.
Ethers, parachors and refractivities of, 616.
preparation of, 617.
"β"-7-Ethoxycholesterol, and its benzoate, 1802.
Ethoxydihydrothionaphthen sulphone, 1617.
2-Ethoxy-4-(4-dimethylaminostyryl)-6-methylpyrimidine, 2151.
2-Ethoxy-3:6-dimethylpyrazine, 4-oxide, and 2-chloro-, 1861.
2-Ethoxydiphenyl ether-5:4'-dialdehyde, 2173.
1-Ethoxyhexylideneaminoacetonitrile, 1970.
α-(1-Ethoxyhexylideneamino)-β-benzoyloxyacrylonitrile, 1970.
1-(α'-Ethoxyhexylideneamino)-β-hydroxyacrylonitrile, potassium salt, and 2:4-dinitrophenylhydrazone, 1970.
2-Ethoxy-6-methyl-3-chloromethylpyrazine, 1861.
11-Ethoxy-5-methyl-5:11-dihydroquinoline, 11-amino-, 921.
Ethoxymethylenemalonic acid, diethyl ester, reaction of, with arylamines, 893.
4-Ethoxymethylenethiazol-5-one, 2-mercapto-, 204.
2-Ethoxy-6-methyl-3-ethoxymethylpyrazine, 1861.
2-Ethoxy-6-methyl-3-hydroxymethylpyrazine, 1862.
2-Ethoxy-3-methylquinoxaline, and its picrate, 522.
3-Ethoxy-2-methylquinoxaline 1-oxide, 522.
***p*-Ethoxyphenylacetic acid**, ethyl ester, preparation of, 152.
2-*p*-Ethoxyphenyl-1:1-di-*n*-propoxyphenylethylene, 155.
***N*¹-*p*-Ethoxyphenyl-*N*⁵-*iso*propyl-*N*⁵-*n*-butyldiguanide**, and its hydrochloride, 1652.
***N*¹-*p*-Ethoxyphenyl-*N*⁵-*iso*propyldiguanide** hydrochloride, 1635.
β-Ethoxypropionylpyruvic acid, ethyl ester, preparation of, 1297.
2-(3'-Ethoxypropyl)*cyclo*hexanone, and its derivatives, 1374.
2-(3'-Ethoxypropyl)*cyclo*hexanone-2-carboxylic acid, ethyl ester, and its 2:4-dinitrophenylhydrazone, 1374.
***trans*-2-(3'-Ethoxypropyl)*cyclo*hexylamine**, and its derivatives, 1374.
***cis*-2-(3'-Ethoxypropyl)*cyclo*hexylbenzamide**, 1375.
***trans*-Ethoxypropyl*cyclo*hexylformamide**, 1375.
2-(3'-Ethoxypropyl)pimelic acid, 1374.
2-Ethoxypyrazines, oxidation of, with hydrogen peroxide, 1859.
2-Ethoxypyridine 1-oxide, and its derivatives, 1866.
2-Ethoxyquinoline 1-oxide, and its derivatives, 1865.
3-Ethoxyquinoxaline 1-oxide, 521.
3-Ethoxyquinoxaline, 2-chloro-, and 2-hydroxy-, 522.
Ethyl allyl sulphilimine, 2-chloro-, 2179.
3-chloroallyl sulphide, 2-chloro-, and 2-hydroxy-, 2181.
2-chloro-*n*-propyl sulphide, 2-chloro-, 41.
2-chloro*iso*propyl sulphide, 2-chloro-, 47.
dichloro- and difluoro-phosphonites, 703.
Ethyl ether, pure dry, preparation of, 1163.
Ethyl ether, 2-hydroxy-2'-mercapto-, 43.
Ethyl heptyl sulphide, 2-chloro-, 2178.
2-hydroxypropyl sulphide, 2-hydroxy-, 41.
2-hydroxy*iso*propyl sulphide, 2-hydroxy-, 40.
hydroxypropyl sulphides, 2-hydroxy-, and their bis-*p*-nitrobenzoates, 47.
n-nonyl sulphide, 2-chloro-, 2178.
n-undecyl sulphide, 2-chloro-, and 2-hydroxy-, 2178.
1-Ethylacenaphthyleno(7':8':2:3)-indole, 1248.
5-1'-Ethyl-*n*-amylhydantoin, 2032.
4-1'-Ethyl-*n*-amylthiazole, 5-amino-2-mercapto-, and its 5-acetyl derivative, 2032.
[2-(3-Ethyl-6:7-benzbenzoxazole)][2-(3-ethyl-6:7-benzbenzthiazole)][γβ'-dimethin-2'-(3'-ethyl-6':7'-benzbenzthiazole)]-trimethincyanine *di*iodide, 1882.
[2-(3-Ethyl-6:7-benzbenzthiazole)][2-(3-ethylbenzselenazole)]-[γβ'-dimethin-2'-(3'-ethyl-6':7'-benzbenzthiazole)]trimethincyanine *di*iodide, 1883.
[2-(3-Ethylbenzoxazole)][2-(3-ethylbenzselenazole)][γβ'-dimethin-2'-(3'-ethylbenzoxazole)]trimethincyanine *di*iodide, 1883.
[2-(3-Ethylbenzoxazole)][2-(3-ethylbenzthiazole)][γβ'-dimethin-2'-(3'-ethylbenzoxazole)]trimethincyanine *di*iodide, 1882.
[2-(3-Ethylbenzoxazole)][2'-(3-ethylbenzthiazole)][γ-2''-(3-ethylbenzoxazole)]pentamethincyanine *di*iodide, 695.
[2-(3-Ethylbenzoxazole)][3-(4-ethyldihydro-β-quinindene)]-dimethincyanine iodide, 1898.
[2-(3-Ethylbenzoxazole)][2'-(1-ethyl-6-methylquinoline)]-[γ-2''-(3-methylbenzthiazole)]pentamethincyanine *di*iodide, 695.
[2-(3-Ethylbenzselenazole)][2'-(1-ethylquinoline)][γ-2''-(3-ethylbenzselenazole)]pentamethincyanine *di*iodide, 695.
[2-(3-Ethylbenzthiazole)][2'-(1:6-dimethylquinoline)][γ-2''-(3-ethylbenzthiazole)]pentamethincyanine *di*iodide, 695.
[2-(3-Ethylbenzthiazole)][2'-(3-ethylbenzoxazole)][γ-2''-(3-ethylbenzthiazole)]pentamethincyanine *di*iodide, 695.
[2-(3-Ethylbenzthiazole)][2-(3-ethylbenzselenazole)]-α-anilomethyltrimethincyanine iodide, 1884.
[2-(3-Ethylbenzthiazole)][2-(3-ethylbenzselenazole)][αβ'-dimethin-2'-(3'-ethylbenzselenazole)]trimethincyanine *di*iodide, 1882.
[2-(3-Ethylbenzthiazole)][2-(3-ethylbenzselenazole)][γβ'-dimethin-2'-(3'-ethylbenzthiazole)]trimethincyanine *di*iodide, 1883.
[2-(3-Ethylbenzthiazole)][3-(4-ethyldihydro-β-quinindene)]-dimethincyanine iodide, 1898.
[2-(3-Ethylbenzthiazole)][2'-(3-methylbenzselenazole)][γ-2''-(3-ethylbenzthiazole)]pentamethincyanine *di*iodide, 695.
[2-(3-Ethylbenzthiazole)][2'-(3-methylbenzthiazole)][γ-2''-(3-ethylbenzthiazole)]pentamethincyanine *di*iodide, 694.
Ethyl 2-bromoethyl ketone, 1-chloro-, 280.
Ethylcarbamic acid, 2-chloro-, 3-chloroallyl ester, 2182.
N-nitro-2-chloro-, *N*-nitroso-2-bromo-, methyl esters, and *N*-nitroso-2-chloro-, ethyl ester, 2320, 2321.
2-Ethylcarbamylphenylthioacetic acid, 84.
Ethyl 2-chloroethyl ketone, 1-chloro-, 280.

3-Ethylcinnoline, 4-hydroxy-, 2319.
Ethylcyanamide, 2-chloro-, 2321.
1′-Ethyl-1′:5′-diaza-2:3-pentamethylenequinoxaline, 781.
Ethyldicyandiamide, 1633.
Ethyldi-(2-fluoroethyl)amine, 2-chloro-, and its picrate, 2176.
Ethyldimethylsulphonium salts, olefin formation from, 2072.
Ethyl-1:2-diphosphonic acid, tetraethyl ester, 702.
Ethylene, catalytic reaction of, with benzene, 73.
Prins reaction with, 89.
Ethylene, *tetra*iodo-, reaction of, with bromine trifluoride, 2188.
Ethylenes, photochemical reactions of, with phenanthraquinone and with 1:2:3-triketones, 2126.
Ethylene dinitroamine. See *s*-Bisnitroaminoethane.
Ethylene glycol bisfluoroacetate, 1779.
Ethylene sulphide, reactions of, 1894.
***NN*-Ethylenebis*tri*chloroacetamidine**, and its salts, 305.
1:3-*endo*Ethylene-1:2:3:4-tetrahydronaphthalene, and its sulphonamido-derivative, 979.
Ethylenic compounds, parachors and refractivities of, 658.
Ethylguanidine sulphate, 1642.
2-Ethyl-*n*-hexanal cyanohydrin, and its hydrochloride, 2032.
2:4-Ethylidene D-sorbitol, and its acetyl derivatives, 1935.
2-Ethylindole, picrate, 275.
Ethylmalonic dideuteracid, 1088.
Ethylmercuric iodide, *penta*fluoro-, 2190.
***o*-Ethylphenylcarbamic acid**, ethyl ester, 878.
Ethylphosphonic acid, diethyl ester, 702.
Ethylphosphonic acid, 2-fluoro-, diethyl ester, 702, 703.
3-Ethyl-2-*n*-propylcinchoninic acid, 109.
***N*¹-Ethyl-*N*³-*iso*propyldicyandiamide**, 1650.
[2-(1-Ethylquinoline)][2-(3-ethylbenzselenazole)][γβ′-dimethin-2′-(1′-ethylquinoline)]trimethincyanine *di*iodide, 1882.
[2-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine iodide, 1884.
[4-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine iodide, 1883.
[2-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)][γβ′-dimethin-2′-(3′-ethylbenzselenazole)]trimethincyanine *di*iodide, 1886.
[2-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)][αβ′-dimethin-2′-(3′-ethylbenzthiazole)]trimethincyanine *di*iodide, 1882.
[4-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)][αβ′-dimethin-2′-(3′-ethylbenzthiazole)]trimethincyanine *di*iodide, 1881.
[2- and 4-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)][γβ′-dimethin-2′-(3′-ethylbenzthiazole)]trimethincyanine *di*iodides, 1885.
[2-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)][γβ′-dimethin-2′-(1′-ethylquinoline)]trimethincyanine *di*iodide, 1882.
[2-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)][γβ′-dimethin-4′-(1′-ethylquinoline)]trimethincyanine *di*iodide, 1886.
[4-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)][γβ′-dimethin-4′-(1′-ethylquinoline)]trimethincyanine *di*iodide, 1882.
[4-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)][γβ′-dimethin-2′-(3′-ethyl-Δ²-thiazoline)]trimethincyanine *diper*chlorate, 1886.
[2- and 4-(1-Ethylquinoline)][3-(4-ethyldihydro-β-quinindene)]-dimethinecyanine iodides, 1897.
[2-(1-Ethylquinoline)][4-(1-ethylquinoline)][γβ′-dimethin-2′-(1′-ethylquinoline)]trimethincyanine *di*iodide, 1880.
[4-(1-Ethylquinoline)][2-(3-ethyl-Δ²-thiazoline)]-γ-anilomethyltrimethincyanine iodide, 1885.
[4-(1-Ethylquinoline)][2-(3-ethyl-Δ²-thiazoline)][γβ′-dimethin-2′-(3′-ethylbenzthiazole)]trimethincyanine *di*iodide, 1886.
[4-(1-Ethylquinoline)][2-(3-ethyl-Δ²-thiazoline)][γβ′-dimethin-4′-(1′-ethylquinoline)]trimethincyanine *di*iodide, 1883.
[4-(1-Ethylquinoline)][2-(3-ethyl-Δ²-thiazoline)][αβ′-dimethin-2′-(3′-ethyl-Δ²′-thiazoline)]trimethincyanine *di*perchlorate, 1882.
[4-(1-Ethylquinoline)][2-(3-ethyl-Δ²-thiazoline)][γβ′-dimethin-2′-(3′-ethyl-Δ²′-thiazoline)]trimethincyanine *diper*chlorate, 1886.
[4-(1-Ethylquinoline)][2-(3-ethyl-Δ²-thiazoline)]trimethincyanine iodide, 1887.
[2- and 4-(1-Ethylquinoline)][2-(4-methyl-3-ethylthiazole)]-γ-anilomethyltrimethincyanine iodides, 1884.
[2-(1-Ethylquinoline)][2-(4-methyl-3-ethylthiazole)]trimethincyanine iodide, 1887.
[4-(1-Ethylquinoline)][2-(4-methyl-3-ethylthiazole)]trimethincyanine iodide, 1887.
***O*-Ethylrepandine *di*methiodide**, 2173.
α-Ethylstilbene, photochemical reaction of, with phenanthraquinone, 2128.
1-Ethyl-1:2:3:4-tetrahydro-1:4:9:10-tetra-aza-anthracene, and its dihydrochloride, 781.
[2-(3-Ethyl-Δ²-thiazoline)][2-(3-ethylbenzthiazole)]-α-anilomethyltrimethincyanine iodide, 1885.
[2-(3-Ethyl-Δ²-thiazoline)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine iodide, 1884.
[2-(3-Ethyl-Δ²-thiazoline)][2-(3-ethylbenzthiazole)][αβ′-dimethin-2′-(3′-ethylbenzthiazole)]trimethincyanine *di*iodide, 1883.
[2-(3-Ethyl-Δ²-thiazoline)][2-(3-ethylbenzthiazole)][γβ′-dimethin-2′-(3′-ethylbenzthiazole)]trimethincyanine *di*iodide, 1886.
[2-(3-Ethyl-Δ²-thiazoline)][2-(3-ethylbenzthiazole)][γβ′-dimethin-2′-(3′-ethyl-Δ²′-thiazoline)]trimethincyanine *diper*chlorate, 1885.
[2-(3-Ethyl-Δ²-thiazoline)][2-(3-ethylbenzthiazole)]trimethincyanine iodide, 1887.
[2-(3-Ethyl-Δ²-thiazoline)][2-(4-methyl-3-ethylthiazole)]-γ-anilomethyltrimethincyanine iodide, 1885.
[2-(3-Ethyl-Δ²-thiazoline)][2-(4-methyl-3-ethylthiazole)][γβ′-dimethin-2′-(3′-ethyl-Δ²′-thiazoline)]trimethincyanine *diper*chlorate, 1885.
[2-(3-Ethyl-Δ²-thiazoline)][2-(4-methyl-3-ethylthiazole)]trimethincyanine iodide, 1887.
β-Ethylthioacrylic acid, α-amino-, hexoyl derivative, and its ethyl ester, 1967.
β-Ethylthioacrylylbenzylamide, α-amino-, hexoyl derivative, 1968.
***N*-(β-Ethylthioacrylyl)glycine**, *N*-α-amino-, hexoyl derivative, 1968.
***N*-(β-Ethylthioacrylyl)-D-penicillamine**, *N*-α-amino-, hexoyl derivative, 1968.
β-Ethylthioacrylyl-*p*-toluidide, α-amino-, hexoyl derivative, 1968.
***N*-Ethylthiobenzamide**, *N*-2-hydroxy-, 1923.
2-Ethylthio-4-benzylidenethiazolone, 1059.
1-(Ethylthio)-2-(3′-chloroallylthio)ethane, 1-2′-chloro-, and 1-2′-hydroxy-, 2181.
2′-(Ethylthio)diethyl ether, 2-mercapto-2′-2-hydroxy-, 44.
2-Ethylthio-4-ethoxymethylenethiazolone, 1060.
2-(Ethylthio)ethylcarbamic acid, 2-2-chloro-, and *N*-nitroso-2-2-chloro-, methyl esters, 2320.
2-Ethylthio-4-hydroxymethylenethiazolone, 1060.
Ethylthiol, 2-amino-, 2-benzoyl derivative, 1924.
3-Ethylthio-6-methylpyridazine, 2200.
2-2′-Ethylthio-1-methylvinylbenzthiazole methiodide, 689.
4-(Ethylthio)phenylarsonic acid, 4-2-hydroxy-, 375.
***p*-(Ethylthio)phenyl*di*chloroarsine**, *p*-2-chloro-, 374.
α-(2-Ethylthio)propaldehyde, α-2-hydroxy-, and its diethylacetal, 40.
β-Ethylthiopropionic acid, 1969.
2-Ethylthiopyridine, 5-amino-, and its hydrochloride, and 5-nitro-, 1944.
2-2′-Ethylthiovinylbenzoxazole methiodide, 689.
2:2′-Ethylthiovinylbenzthiazole, metho-salts, 689.
2-2′-Ethylthiovinylquinoline, metho-salts, 689.
Ethynylpropenylcarbinol, kinetics of acid-catalysed rearrangement of, in solvent mixtures, 1982.
Evodia elleryana, ketone from, 2005.
Evodione, constitution of, 2005.

F.

Fabiatrin *hexa*acetate and ***di*hydrate**, 1672.
synthesis of, 1671.
Films, soluble, at air–liquid and liquid–liquid interfaces, vertical-plate measurements with, 930.
Filters, column, revivable, for spent catalysts, 1091.
Fluoranthene, synthesis of, 1139.
Fluorene, condensation of, with acetone, 1137.
Fluorene-1-carbonylacetoacetic acid, 9-bromo-, and 9-chloro-, ethyl esters, 1141.
3-(Fluorene-1-carbonyl)butan-2-one, 3-9-chloro-, 1141.
Fluorene-1-carboxylic acid, and its amide, 1140.
Fluorene-1-carboxylic acid, 9-bromo-, 9-chloro-, and 9-iodo-, and their derivatives, 1140, 1141.

9-Fluorenol-1-carboxylic acid, 1140.
Fluorenone-1-carboxylic acid, ethyl ester, and its derivatives, 1141.
Fluorine compounds, toxic, containing C–F link, 1773.
Fluorophosphonic acid, di*iso*propyl ester, 695.
esters, 1010.
Formaldehyde, yield of, from periodate oxidation of carbohydrates, 994.
Formamidines, *s*-disubstituted, 1716.
Formic acid, detection of, in mixtures with aliphatic monobasic acids, 1015.
ethyl ester, formylation of amines with, 1457.
Formic acid, chloro-, 3-chloroallyl ester, 2182.
fluoro-, ethyl ester, 1778.
ethyl and phenyl esters, 2186.
2-Formyl-4-carbomethoxyphenoxyacetic acid, 3-hydroxy-, and its ethyl ester, and its 2:4-dinitrophenylhydrazone, 116.
5-Formylcoumaran, 6-hydroxy-, and its 2:4-dinitrophenylhydrazone, 2257.
N-Formyldi-(2-chloroethyl)amine, *N*-chloro-, 2174.
2-Formyl-3:6-dimethylcoumarone, and its 2:4-dinitrophenylhydrazone, 2260.
6-Formyl-4:7-dimethyl-2-*iso*propylhydrindan-5-one, and its disemicarbazone, 167.
3-Formyldiphenylarsonous acid, and its 2:4-dinitrophenylhydrazone, 2209.
3-Formyldiphenylcyanoarsine, 2211.
2-Formylethylideneaniline, 2:4′-*di*nitro-, 2026.
2-Formylethylidenetoluidines, *mono-* and *di*-nitro-, 2026.
5-Formyl-3-methylcoumaran, 6-hydroxy-, and its 2:4-dinitrophenylhydrazone, 2259.
2-Formyl-3-methylcoumarone, 6-hydroxy-, and its derivatives, 2258.
2-Formyl-4-methylphenoxyacetic acid, 5-hydroxy-, 5-benzyl derivative, and its ethyl ester, 2258.
2-Formylphenoxyacetic acid, 5-hydroxy-, 5-benzyl derivative, and its ethyl ester, 2257.
Fractionating agents for starch, 1687.
Friedel–Crafts reaction in preparation of halogenated aliphatic ketones, 278.
Fumaric acid, esters, 665.
Furan, derivatives, formation of, from sucrose, 155.
Furano-compounds, 115, 2254, 2260.
Furano(2′:3′:6:7)dihydrobenzfuran-3-one, and its semicarbazone, 895.
N-2-Furfuryl-*N*′-methylacetamidine, 1521.
2-(2′-Furyl)-Δ^2-pyrroline, and its picrate, 188.

G.

ε-Galactan, and its derivatives, 775.
4-D-Galactopyranosidamino-2-methylthiopyrimidine, 6-amino-, 962.
Gallium, reaction of, with nitrosyl chloride, 1955.
Gallium *tri*chloride, reaction of, with nitrosyl chloride, 1955.
(−)-Gallocatechin gallate, 2253.
Gases, adsorption of, on minerals, 135.
solubility of, measurement of, 2033.
solution and diffusion of, in polystyrene at high pressures, 1541.
Geranamide, spectrum of, infra-red absorption, 1415.
Ginkgetin, structure of, 2138.
Glucamine, deamination of, to 1:4-anhydrosorbitol, 299.
9-D-Glucopyranosidoadenine, synthesis of, 965.
9-D-Glucopyranosido-2-methylthioadenine, 966.
4-D-Glucosidamino-5-(2′:5′-*di*chlorobenzeneazo)pyrimidine, 6-amino-, and its 4-tetra-acetyl derivative, 967.
4-D-Glucosidamino-2-methylthiopyrimidine, 6-amino-, and its penta-acetyl derivative, 966.
4-D-Glucosidaminopyrimidine, 6-amino-, 966.
5:6-*di*amino-, and its 4-tetra-acetyl derivative, 967.
2-β-Glucosidoxy-5-methoxybenzoic acid, methyl ester, hemihydrate, 2222.
4- and 6-Glucuronosidogalactoses, 1141.
Glycerides, natural, mixed, configuration of, 722.
X-ray and thermal examination of, 985.
Glycerol, photochemical oxidation of, by dichromate, 2119.
4-Glycofuranosidaminopyrimidines, preparation of, 957.
Glycogen, experiments with, 995.
methylated, diffusion and ultracentrifugal characteristics of, 1567.
Glycosides, synthesis of, 1671, 2220.
Glyoxal, bond strengths in, 404.
sulphate, preparation of, 764.
Glyoxaline, 4(5)-amino-, and 4(5)-amino-2-mercapto-, 4(5)-benzoyl derivatives, 1266.
Glyoxalines, 1960.
Gomberg reaction, 349.
Grignard reagents, effect of impurities in magnesium on formation of, 1597.
Guanidine, amino-, reaction of, with isatin, 2314.
2-Guanidinobenziminazole, and 5-chloro-, and their salts, 1368.
2-Guanidinobenziminazole, 5:6-*di*chloro-, and its salts, 1369.
2-Guanidino-5:6-dimethoxybenziminazole, and its salts, 1368.
2-Guanidino-5:6-dimethylbenziminazole, and its salts, 1369.
2-Guanidino-5-methoxybenziminazole, and its salts, 1368.
2-Guanidino-5-methylbenziminazole, and its salts, 1368.
2-Guanidino-6-methylpyrimidine, 4-hydroxy-, 592, 596.
Guanine, dissociation constants of, 765.
Guanosine, synthesis of, 1685.
Guanylthioureas, conversion of, into diguanides, 1645.
Guanylurea formate, 1369.
Gum gatto. See Carob gum.

H.

Halogens, kinetics of addition of, to unsaturated compounds, 980.
kinetics of substitution by, in aromatic compounds, 100.
parachors and refractivities of, 644.
Halogen compounds, bond strengths in, 404.
Halogeno-ketones, 272, 276, 278.
Heat of ionisation of organic acids, 1016, 1019.
n-Heptane, *hexadeca*fluoro-, spectrum of, infra-red absorption, 1432.
3:4-*cyclo*Heptenoi*so*oxazole, 169.
Hept-2-enyl cyanide, 5-nitro-, 230.
n-Heptoic acid, adsorption of, from solution, by calcined and hydrated alumina powders, 969.
Heptyl cyanide, 5-nitro-, 230.
α-*n*-Heptylpelargonic acid, α-amino-, 1388.
p-*n*-Heptylsulphonylbenzylammonium chloride, 382.
p-*n*-Heptylsulphonylphenyl cyanide, 383.
Heterocyclic compounds, chemistry of, 360.
syntheses of, 1537.
by Hofmann reaction, 523.
p-*n*-Hexadecylsulphonylbenzylammonium chloride, 382.
p-*n*-Hexadecylsulphonylphenyl cyanide, 383.
Hexadeuterobenzene, spectrum of, absorption, ultra-violet, 433.
fluorescence, ultra-violet, 440.
*cyclo*Hexa-1:3-dione, as reagent for aldehydes, 1371.
3-Hexahydrobenzamido-2:4-diketopyrrolidine, 1959.
cis- and *trans*-Hexahydrochrysenes, 1001.
Hexahydrodi*chano*strychnidine, 1665.
Hexahydrophenanthridone, 1294.
Hexamethyl*iso*cyanidoferrous chloride *tri*hydrate, structure of, 63.
n-Hexane, thermal decomposition of, 2226.
n-Hexane, 1-nitro-, preparation and physical properties of, 1847.
*cyclo*Hexane, *hexa*chloro-, stereoisomers, spectra of, infra-red absorption, 1420.
1:2-*di*chloro-1-nitro- and -1-nitroso-, 2321.
*dodeca*fluoro-, spectrum of, infra-red absorption, 1432.
*cyclo*Hexanol, as fractionating agent for starch, 1687.
*cyclo*Hexanone, 2-chloro-, oxime, 2321.
5:6-*cyclo*Hexenopyrimidine, 2-cyanoamino-4-hydroxy-, 579.
Hex-2-enyl cyanide, 5-nitro-, 230.
Hex-3-en-5-yne, 2-hydroxy-, 2-acetyl derivative, hydrolysis of, 798.
n- and *iso*-Hexœstrols, 686.
DL-*N*-Hexoylcysteine, 1969.
3-Hexoyl-3-methylbutanecarboxylic acid, 1745.
*cyclo*Hexyl bromide, chloride, and iodide, preparation and properties of, 1811.
N-*cyclo*Hexyl-1-amidino-*n*-heptane, preparation of, 308.

2-*cyclo*Hexylamino-4-(4-dimethylaminostyryl)-6-methylpyrimidine, 2151.
***cyclo*Hexylaminophosphonic acid**, dibenzhydryl ester, 1110.
4-*cyclo*Hexylbut-2-enyl cyanide, 4-1-nitro-, 230.
4-*cyclo*Hexylbutyl cyanide, 4-1-nitro-, 230.
***cyclo*Hexylcarbamic acid**, ethyl and methyl esters, 881.
2-*n*-Hexylcinchoninic acid, and 6-bromo-, and 6:8-*di*chloro-, 109.
***cyclo*Hexyldicyandiamide**, 1633.
***N*-*cyclo*Hexyl-*N*′-ethylacetamidine**, and its hydrochloride, 1521.
***N*-*cyclo*Hexyl-*N*′-ethylpropionamidine**, and its hydrochloride, 1521.
***N*-*cyclo*Hexyl-*N*′-methylacetamidine**, 1521.
hydrochloride, 1522.
α-*cyclo*Hexylmethylaminobutyric acid, and its derivatives, 316.
α-*cyclo*Hexylmethylamino-β-hydroxybutyric acid, 316.
2-*cyclo*Hexyl-6-methylheptane, 48, 49.
***N*-*cyclo*Hexylphenylacetamidine**, preparation of, 308.
2-*n*-Hexylquinoline, and 6-bromo-, 6:8-*di*chloro-, and 6:8-*di*chloro-4-hydroxy-, and their picrates, 109.
p-*n*-Hexylsulphonylbenzylammonium chloride, 382.
p-*n*-Hexylsulphonylphenyl cyanide, 383.
***N*-*cyclo*Hexylsydnone**, 2309.
4-*n*-Hexylthiazole, 5-amino-2-mercapto-, and its derivatives, 2032.
***n*-Hexylthiol**, preparation and properties of, 1822.
Hofmann reaction in synthesis of heterocyclic compounds, 523.
Hopkins Memorial Lecture, 713.
Hydrazine, anhydrous, preparation of, 1458.
Hydrobromic acid, See under Bromine.
Hydrocarbons, aromatic, catalysed gas-phase reactions of, 73, 1700, 2154.
binding energies in, 1448.
carcinogenic, oxidation of, with osmium tetroxide, 170.
chemistry of, 531.
fluorinated, spectra of, infra-red absorption, 1428, 1432.
formation of organic peroxides from, 339.
Hydrochloric acid. See under Chlorine.
Hydrogen atoms, associating effect of, 874.
bonding, in 4-triacetyl-D-xylosidaminopyrimidines, 2265.
ions, nature of, in aqueous and non-aqueous solvents, 1976.
isotopic differentiation of, in molecular asymmetry, 1085.
solubility and diffusion of, in polystyrene, 1541.
Hydrogen bromide. See Hydrobromic acid under Bromine.
chloride. See Hydrochloric acid under Chlorine.
*per*oxide, bond energies in, 331.
oxidation with, of 2-hydroxyquinoxaline, and its derivatives, 519.
reaction of, with symmetrical triketones, 50.
selenide, photochemical oxidation of, 766.
Hydrogen–nitrogen–oxygen linking, 874.
Hydroxamic acids, 1864.
Hydroxy-carbonyl compounds, 1674.
Hyperconjugation, 17.

I.

2-Imino-3-phenyl-3-2′-hydroxyethyltetrahydrofuran, 808.
Indan-3-one-1-carboxylic acid, and its derivatives, 980.
Indigo, 5:6:5′:6′-*tetra*hydroxy-, synthesis of, and its tetraacetyl derivative, 1244.
Indium, reaction of, with nitrosyl chloride, 1955.
Indium *tri*bromide and *mono*chloride, 1958.
Indole, derivatives, polycyclic, action of nitric acid on, 1247.
Indole, 5:6-*di*hydroxy-, synthesis of, and its derivatives, 2223.
Indoles, formation of, from phenacylarylamines, 847, 858.
Indoles, hydroxy-, synthesis of, 1605.
Indole-2-carboxylic acid, 6-hydroxy-, 1608.
7-hydroxy-, and its 7-benzyl derivative, 1608.
Indole-(2′:3′:3:4)-coumarin, 7-hydroxy-, and its diacetyl derivative, 1674.
***iso*Indolinone** derivatives from aniline, 1249.
1:3:4-Indotriazine, 2-amino-, and its salts and derivatives, 2314, 2317.
Insulin, adsorption of water vapour on, 1083.
Inter-halogen compounds, chemistry of, 2135.
Iodine, molecular, solvolytic ionisation of, 1051.
solutions, alkaline, oxidation by, of aldoses, 810.
Periodates, oxidation by, applied to carbohydrates, 992.
Ion-exchange apparatus, 1273.
Ion-exchangers, 1273.
Ionisation constants of heterocyclic bases, 2240.
Isatin condensation of, with barbituric acid, 552.
anti- and *syn*-β-guanylhydrazones, and their salts and derivatives, 2315.
reaction of, with aminoguanidine, 2314.
Isatin *syn*-β-guanylhydrazone-5-sulphonic acid, 2316.
Isomerisation, bimolecular, 1.
Isoprene, action of hydrogen chloride on, 530.

K.

Karanjic acid, synthesis of, and its acetate, 115.
Karanjin, synthesis of, 894.
Kaurene, identity of, with podocarprene, 1888.
Keten, spectrum of, infra-red absorption, 1416.
7-Keto-3(β)-acetoxy-5-*allo*cholanic acid, methyl ester, 1042.
α-Keto-β-acetylbutyrolactone, 1297.
5-Keto-2-*n*-amyl-4-benzylthiomethylene-4:5-dihydro-oxazole, 1968.
5-Keto-2-*n*-amyl-4-ethylthiomethylene-4:5-dihydro-oxazole, 1968.
1-Keto-4:5-benz-$\Delta^{4,2}$-hexahydroazulene, and its semicarbazone, 169.
2-Keto-4-benzoyloxy-1-benzoyl-Δ^{3}-pyrroline, 3-amino-, 3-benzoyl derivative, 1959.
2-Keto-4-benzoyloxy-Δ^{3}-pyrroline, 3-amino-, 3-benzoyl derivative, 1959.
1-Keto-3-(2′:4′:6′-*tri*bromophenyl)-2-methyltetrahydrophthalazine-4-acetic acid, and its anilide, 598.
α-Keto-β-(β′-carbethoxypropionyl)butyrolactone, 1298.
3-Keto-2-carbomethoxy-4-methoxy*cyclo*heptatrienylacetic acid, methyl ester, 1051.
3-Keto-2-carboxy*cyclo*heptatrienylacetic acid, 4-hydroxy-, 1051.
1-Keto-3-(2′-chloro-5′-nitrophenyl)-2-methyltetrahydrophthalazine-4-acetic acid, and its derivatives, 208.
1-Keto-3-(2′-chlorophenyl)-4-methyltetrahydrophthalazine, 1028.
1-Keto-3-(3′-chlorophenyl)-4-methyltetrahydrophthalazine, 600.
1-Keto-3-(2′-chlorophenyl)-2-methyltetrahydrophthalazine-4-acetic acid, 1027.
1-Keto-3-(2′-chlorophenyl)tetrahydrophthalazine, 1028.
α-Keto-β-(β′-chloropropionyl)butyrolactone, 1298.
Ketocholanic acids, reaction of, with ethyl bromo- and chloroacetates, 1358.
7-Keto-5-*allo*cholanic acid, 3(β)-hydroxy-, 1042.
6-Ketocholestane, derivatives of, 1032.
1-Ketodecahydroazulene, and its semicarbazone, 169.
5-Keto-4:7-dimethyl-2-*iso*propyl-Δ^{4}-tetrahydroindane, and its derivatives, 167.
2-Keto-1-ethoxy-1:2-dihydroquinoline, preparation of, 1866.
α-Keto-β-(β′-ethoxypropionyl)butyrolactone, 1298.
4-Keto-1:3-*endo*ethylene-1:2:3:4-tetrahydronaphthalene, and its derivatives, 977, 979.
4-Keto-2-ethylthionaphtheno-(2′:3′:5:6)-1:3-oxazine, 81.
4-Keto-1:2:3:4:10:11-hexahydro*cyclo*pentindene, and its derivatives, 979.
2-Ketohexamethyleneimine, preparation of, 1518.
β-2-Keto*cyclo*hexylbenzylmalonic acid, and its derivatives, 2014.
β-2-Keto*cyclo*hexylbenzylmalonic anhydride, and its hydrogenation product, 2013, 2015.
β-2-Keto*cyclo*hexyl-*p*-methoxybenzylmalonic acid, 2016.
β-2-Keto*cyclo*hexyl-*p*-methoxybenzylmalonic anhydride, 2016.
β-2-Keto*cyclo*hexyl-β-*p*-methoxyphenylpropionic acid, and its ethyl ester and its oxime, 2016.
β-2-Keto*cyclo*hexyl-β-phenylpropionic acid, ethyl ester, oxime, 2015.
4-Keto-1-methoxy-3-(2′-chloro-5′-nitrophenyl)-3:4-dihydrophthalazine, 208.
4-Keto-1-methoxy-3-(2′-chlorophenyl)-3:4-dihydrophthalazine, 1029.
α-Keto-β-(β′-methoxypropionyl)butyrolactone, and β-chloro-, 1298.
α-Keto-β-(β′-methoxypropionyl)-γ-phenylbutyrolactone, 1298.
α-Keto-β-(β′-methoxypropionyl)-γ-valerolactone, 1298.
2-Keto-1-methyl-3-chloromethyl-1:2-dihydroquinoxaline, 522.

1-Keto-13-methyl-$\Delta^{11:12}$-dodecahydrophenanthrene, and its derivatives, 163.
4-Keto-2-methyl-3:4-dihydrothionaphtheno(2′:3′:5:6)pyrimidine, 81.
2-Keto-5-methylhexamethyleneimine, 1519.
5-Keto-2-methyl-4-(2′-nitro-5′-acetoxybenzylidene)-4:5-dihydro-oxazole, 1607.
5-Keto-2-methyl-4-(2′-nitro-5′-hydroxybenzylidene)-4:5-dihydro-oxazole, 1607.
6-Keto-2-methylthionaphtheno(3′:2′:4:5)-1:3-oxazine, 81.
5-Keto-4-(2′-nitro-6′-acetoxybenzylidene)-2-methyl-4:5-dihydro-oxazole, 1609.
1-Keto-3-(4′-nitro-2′:5′-dimethoxyphenyl)-2-methyltetrahydrophthalazine-4-acetic acid, 282.
Ketones, constitution and physical properties of, 610.
formation of, from α-amino-acids, 176.
from semicarbazones with nitrous acid, 2319.
halogenated, 272, 276, 278.
hydroaromatic, fused-ring, synthesis of, 162.
non-enolisable, fission of, by potassium *tert.*-butoxide, 1408.
αβ-unsaturated, cyclic, reactions of, 996.
halogen addition to, 980.
2:5-Keto-3-phenyl*iso*indolinopyrazolidocoline, 1251.
5-Keto-2-phenyl-4-methyl-4:5-dihydroiminazole, and its derivatives, 735.
1-Keto-3-phenyl-4-methyltetrahydrophthalazine, 1251.
1-Keto-3-phenyl-2-methyltetrahydrophthalazine-4-acetic acid, 1250.
α-Keto-β-propionylbutyrolactone, 1298.
α-(2-Keto-4-*iso*propyl*cyclo*pentyl)propionic acid, and its semicarbazone, 168.
6-Ketositostane, derivatives of, 1043.
2-Keto-4-thio-3′-methyl-3-ethyl-5:2′-ethylidenebenzthiazolylidenetetrahydrothiazole, 690.
2-6′-Ketothionaphtheno-(3″:2″:4′:5′)-1:3-oxazinyl-2′-thionaphthen, 3-amino-, 3-diacetyl derivative, and its derivatives, 80.
Ketoxime sulphonates, Beckmann rearrangement of, in presence of ammonia or amines, 1514.

L.

Lanosterol, 988.
Larch wood, ε-galactan of, 774.
Larix decidua, wood, ε-galactan of, 774.
Lectures delivered before the Chemical Society, 243, 386, 713, 1461.
Lepidine, preparation of, 1457.
1-α-Lepidylbenztriazole, 923.
Leptospermone, synthesis and derivatives of, 383.
Leuconostoc mesenteroides. See *Betacoccus arabinosaceus*.
Levan, structure of, from sucrose, 1560.
Lewisite, molar polarisation of, 1208.
***iso*Lewisite**, molar polarisation of, 1208.
Linalol, spectrum of, infra-red absorption, and structure, 1415.
Linkings, double, addition of thiol-compounds to, 1683.
factors influencing strength of, 398.
Linoleic acid, methyl ester, autoxidation of, 2275.
Liversidge Lecture, 1461.

M.

Magnesium, effect of metallic impurities in, on formation of Grignard reagents, 1597.
Maize starch. See under Starch.
Maleic acid, esters, 664.
Mandelonitrile, *p*-bromo-, and *o*-chloro-, benzoate, 1255.
Manganese :—
Manganous sulphate as catalyst in chromic acid oxidation of hydrobromic acid, 1376.
Mannitol, reaction of, with hydrochloric acid, 2204.
Mannitol, 1:6-*di*bromo-, and its 2:3:4:5-tetra-acetyl derivative, 2202.
9-D-Mannopyranosidoxanthine, synthesis of, 523.
Mannose, preparation of, 1989.
1-D-Mannosidoglyoxaline-4:5-dicarboxyamide, 524.
9-D-Mannosidoxanthine, 524.
Melanin, and its precursors, 1244.
Melanins, chemistry of, 2223.
Memorial Lecture, Sir Frederick Gowland Hopkins, 713.
Mepacrine, conversion of, into thioacridones, 1181.
resolution of, and its salts, 99.
Mercapto-acids, tertiary, preparation of, 1683.
Mesaconic acid, esters, 665.
Mesquite gum, constitution of, 1141, 1146.
Mesquitic acid, and its acetate, methylation of, 1152.
preparation of, 1144.
Metals, and their chlorides, action of nitrosyl chloride on, 1952.
complex compounds of, with dimethylglyoxime, 378.
Metal electrodes, 740, 749, 752, 756, 759.
Metallic halides, reaction of, with bromine trifluoride, 2135.
Metanethole, 1985.
Methane, chlorofluoro-derivatives, spectra of, infra-red absorption, and thermodynamics, 1422.
iodo*tri*fluoro-, 2190.
nitro-, condensation of, with aldehydes, 1907.
Methanesulphonyl-. See also Methylsulphonyl-.
5-Methanesulphonyl 2-chloro 1:4:3:6-dianhydromannitol, 2207.
Methanol. See Methyl alcohol.
4-Methoxy-7-acetoacetylchromone, 6-hydroxy-, 2263.
4-Methoxy-7-acetoacetylcoumaran, 6-hydroxy-, 2264.
4-Methoxy-5-acetoacetylcoumarone, 6-hydroxy-, 2262.
2-Methoxyacetophenone, 5-hydroxy-, and its 5-benzyl derivative, 2142.
6-Methoxyacetophenone, 2:3-*di*hydroxy-, dibenzyl derivative, 2141.
preparation of, 2140.
2:6-*di*hydroxy-, 2:3-dianisyl derivative, 2142.
3-Methoxy-4-acetoxycinnamic acid, 2-nitro-α-amino-, α-acetyl and α-benzoyl derivatives, azlactones of, 377.
2-Methoxy-6-acetoxyphenoxyacetic acid, 1611.
6-Methoxy-3-acetylacetophenone, 2-hydroxy-, 2141.
4-Methoxy-3-acetylbenzoic acid, 2:6-*di*hydroxy-, methyl ester, and its 2:4-dinitrophenylhydrazone, 2264.
8-Methoxy-4-acetylchroman-3-one, 1611.
4-Methoxy-7-acetylcoumarone, 6-hydroxy-. See *iso*Visnagone.
4-Methoxy-7-acetylcoumarone-2-carboxylic acid, 6-hydroxy-, 2263.
ethyl ester, and its 2:4-dinitrophenylhydrazone, 2263.
5-Methoxyacetyl-2:3-dihydrobenzfuran, 4-hydroxy-, and its semicarbazone, 895.
7-Methoxyacetyl-2:3-dihydrobenzfuran, 4-hydroxy-, 895.
***N*-3-Methoxyacridyl(5)-*p*-aminobenzoic acid**, *N*-8-chloro-, 241.
6(or 7)-Methoxyalloxazine, 1720.
4-*p*-Methoxyanilino-2-γ-diethylaminopropylaminoquinazoline, *di*hydrochloride, 1770.
4-Methoxyanthranilamide, preparation of, 1764.
6-Methoxybenzamide, 2-amino-, preparation of, 1763.
2-Methoxy*meso*benzanthrone, synthesis of, 1088.
5-Methoxybenzoxazolone, 215.
5-Methoxybenzoxazolone-6-sulphonic acid, 215.
3-*m*- and **-*p*-Methoxybenzoyl*meso*benzanthrones**, 2038.
***p*-Methoxybenzoylmethylcarbinol** *p*-nitrobenzoate, 1675.
Methoxy-3:4-benzpyrenes, 173.
1-Methoxy-3-(2′:4′:6′-*tri*bromophenyl)-4-(5″-keto-1″-phenyl-3″-methylpyrazolinylidene-ethylidene)-3:4-dihydrophthalazine, 599.
1-Methoxy-3-(2′:4′:6′-*tri*bromophenyl)-4-methylene-3:4-dihydrophthalazine, and its perchlorate, 599.
1-Methoxy-3-(2′:4′:6′-*tri*bromophenyl)-4-(2″:4″-*di*nitrobenzylidene)-3:4-dihydrophthalazine, 599.
6-Methoxy-4-(α-bromopropionyl)quinoline hydrobromide, 95.
5-Methoxy-2-carbethoxyphenoxyacetic acid, ethyl ester, 1674.
6-Methoxy-4-(3:3:3-*tri*chloro-2-hydroxypropyl)quinoline, 96.
2-Methoxy-1-chloromethylnaphthalene, 6-bromo-, 264.
1-Methoxy-3-(2′-chloro-5′-nitrophenyl)-4-methylene-3:4-dihydrophthalazine, and its perchlorate, 208.
1-Methoxy-3-(2′-chloro-5′-nitrophenyl)-4-(2″:4″-*di*nitrobenzylidene)-3:4-dihydrophthalazine, 208.
1-Methoxy-3-(2′-chlorophenyl)-4-methylene-3:4-dihydrophthalazine, and its perchlorate, 1028.
1-Methoxy-3-(2′-chlorophenyl)-4-(2″:4″-*di*nitrobenzylidene)-3:4-dihydrophthalazine, 1028.
"β"-7-Methoxycholest-4-en-3-one, and its 2:4-dinitrophenylhydrazone, 1803.
"α"-7-Methoxycholesterol, and its esters, 1802.
"β"-7-Methoxycholesteryl acetate and benzoate, 1801, 1802.

7-Methoxychroman-3-one, and its 2:4-dinitrophenylhydrazone, 1611.
8-Methoxychroman-3-one, and its 2:4-dinitrophenylhydrazone, 1611.
3-Methoxycinnamic acid, 2-nitro-α-amino-4-hydroxy-, α-acetyl-4-benzoyl derivative, azlactone of, 377.
4-Methoxycinnamic acid, 2-nitro-α-amino-3-hydroxy-, 2:3-diacetyl derivative, azlactone of, 377.
"β"-7-Methoxycoprostan-3-one, and its 2:4-dinitrophenylhydrazone, 1803.
4-Methoxycoumaran, 6-hydroxy-, and its derivatives, 2263.
5-Methoxy-β-coumaranone-2-carboxylic acid, ethyl ester, 1674.
6′-Methoxycoumarono-(2′:3′:3:4)-coumarin, 7-hydroxy-, and 7:8-*di*hydroxy-, and their derivatives, 1674.
4-Methoxy-5-diazoacetylbenzfuran, 895.
3-Methoxy-1:2:5:6-dibenzanthracene, 173.
2-Methoxy-6-(2-dibutylamino-1-hydroxyethyl)naphthalene, 1-bromo-, *di*picrate, 97.
2′-Methoxydiethyl sulphilimine, 2-chloro-, 2179.
Methoxydihydrothionaphthen sulphone, 1617.
3-Methoxy-9:10-dimethyl-1:2-benzanthracene, 173.
2-Methoxy-5:11-dimethyl*iso*quinindoline, 924.
2-Methoxy-5:11-dimethylquinindolinium chloride, 924.
6-Methoxy-2:3-diphenylquinoxaline, 1720.
1-Methoxy-4-ethoxy-3-(2′-chlorophenyl)-3:4-dihydrophthalazine, 1028.
4′-Methoxyflavone, 5:8-*di*hydroxy-, and its diacetyl derivative, 2143.
synthesis of, 2138.
6-Methoxy-3-formylacetophenone, 2-hydroxy-, preparation of, 2140.
4-Methoxy-3-formylbenzoic acid, 2:6-*di*hydroxy-, methyl ester, and its semicarbazone, 2264.
α-Methoxyhexylideneaminoacetic acid, ethyl ester, 1966.
α-(1-Methoxyhexylideneamino)-β-hydroxyacrylic acid, ethyl ester, potassium salt, 1966.
6-Methoxy-4-(1-hydroxy-2-*N*-piperidylpropyl)quinoline, 95.
5-Methoxyindole, 6-hydroxy-, 2226.
6-Methoxyindole, 5-hydroxy-, and its 5-acetyl derivative, 2226.
6-Methoxylepidine, *N*-oxide, and its salts, 96.
1-α-(6-Methoxylepidyl)benztriazole, 923.
5-Methoxymethoxybenzaldehyde, 2-nitro-4-hydroxy-, 1246.
2-Methoxy-1-methoxymethylnaphthalene, 6-bromo-, 264.
3-Methoxy-1′-methyl-1:2-benzanthracene, 173.
4-Methoxy-2-methyl-6:7-benzquinoline, 1293.
6-Methoxy-20-methylcholanthrene, 173.
7-Methoxy-2-methylchroman-4-one, and its derivatives, 1612.
7-Methoxy-3-methylcoumarin, 4-hydroxy-, and its acetate, 175.
Methoxymethyldi-(2-chloroethyl)amine, 2174.
11-Methoxy-5-methyl-5:11-dihydroquindoline, 11-amino-, 921.
7-Methoxy-3-(3′:4′-methylenedioxyphenyl)coumarin, 4-hydroxy-, and its derivatives, 175.
7-Methoxy-2-methylfurano(2′:3′:5:6)chromone. See *iso*-Visnagin.
2-Methoxy-11-methylquinindoline, and its 6-acetyl derivative, 923.
1-Methoxy-8-α-naphthylsulphonylnaphthalene, 606.
6-Methoxynicotinamidine, salts, 1943.
1-Methoxy-3-(4′-nitro-2′:5′-dimethoxyphenyl)-4-(5″-keto-1″-phenyl-3″-methylpyrazolinylidene-ethylidene)-3:4-dihydrophthalazine, 283.
1-Methoxy-3-(4′-nitro-2′:5′-dimethoxyphenyl)-4-methylene-3:4-dihydrophthalazine, 283.
1-Methoxy-3-(4′-nitro-2′:5′-dimethoxyphenyl)-4-methylphthalazinium *per*chlorate, 283.
1-Methoxy-3-(4′-nitro-2′:5′-dimethoxyphenyl)-4-(2″:4″-*di*nitrobenzylidene)-3:4-dihydrophthalazine, 283.
4-Methoxyphenol-5-sulphonic acid, 2-amino-, 215.
4-Methoxyphenylacetic acid, 2-nitro-3-hydroxy-, 378.
7-Methoxy-3-phenylcoumarin, 4-hydroxy-, and its acetate, 175.
4-Methoxyphenyl 3:4-dimethoxybenzyl ketone, 2-hydroxy-, 175.
γ-(*p*-Methoxyphenyl)-α-ethylbutyramide, 1676.
***m*-Methoxyphenylethylcarbinol**, and its phenylurethane, 2145.
4-*p*-Methoxyphenyl-1-ethyldecahydroquinoline, and its salts, 2016.
***p*-Methoxyphenylethynylcarbinol**, 2037.
***p*-Methoxyphenyl ethynyl ketone**, 2038.
2-(2′-Methoxyphenyl)guanidino-6-methylpyrimidine, 4-hydroxy-2-5′-chloro-, 579.
4-*p*-Methoxyphenyl-3:4:5:6:7-hexahydrocoumarin, 2016.
γ-(*p*-Methoxyphenyl)-α-methylbutyramide, 1676.
***p*-Methoxyphenylpropiolic acid**, dimerisation of, 1267.
α-*p*-Methoxyphenylpropionamide, 1675.
β-*p*-Methoxyphenylpropionylmethylcarbinol *p*-nitrobenzoate and 3:5-*di*nitrobenzoate, 1676.
4-Methoxyphenylpyruvic acid, 2-nitro-3-hydroxy-, 377.
4-*p*-Methoxyphenylsulphonylbenzaldehyde, 602.
1-Methoxy-8-phenylsulphonylnaphthalene, 606.
***p*-Methoxyphenyl *p*-tolyl sulphone**, 602.
6-Methoxy-4-(α-*N*-piperidylpropionyl)quinoline *di*picrolonate, 95.
6-Methoxy-4-propenylquinoline, and its picrate, 96.
β-Methoxypropionylpyruvic acid, methyl ester, preparation of, 1297.
6-Methoxy-4-propylquinoline, and its salts, 95.
1-Methoxypyrene, 173.
2-Methoxypyridine, 5-cyano-, 1945.
4-Methoxy-1:2:2′:3′-pyridoacridine, 5-amino-, and its derivatives, and 5-chloro-, 291.
5-Methoxy-1:2:2′:3′-pyridoacridine, and 4-fluoro-, 291.
5-(2-Methoxypyridyl)methylamine hydrochloride, 1945.
4-Methoxyquinazoline, 6- and 7-nitro-, 364.
5-Methoxyquinazoline, 2:4-*di*hydroxy-, 1763.
6-Methoxyquinazoline, 2:4-*di*chloro-, 1763.
7-Methoxyquinazoline, 2:4-*di*chloro-, and 2:4-*di*hydroxy-, 1764.
8-Methoxyquinazoline, 2:4-*di*chloro-, and 2:4-*di*hydroxy-, 1764.
4-Methoxyquinoline, 6- and 8-nitro-, 1708.
6-Methoxy-8-quinolylacetic acid, ethyl ester, and its salts, 98.
β-6-Methoxy-4-quinolylacrylic acid, 96.
β-6-Methoxyquinolyl(4)alanine, and its dihydrochloride, 89.
6-(6′-Methoxy-8′-quinolylamino)-4-diethylamino-1:3:5-triazine, 2-amino-, and 2-chloro-, and their hydrochlorides, 563.
6-(6′-Methoxy-8′-quinolylamino)-1:3:5-triazine, 2:4-*di*amino-, and its hydrochloride, and 2:4-*di*chloro-, 563.
6-Methoxy-8-quinolyl chloromethyl ketone, and its hydrochloride, 98.
6-Methoxy-8-quinolyl di-*n*-butylaminomethyl ketone, *di*picrate, 99.
6-Methoxy-8-quinolyl diethylaminomethyl ketone, *di*picrate, 99.
6-Methoxy-4-quinolylethylcarbinol, and its salts, 96.
6-Methoxy-4-quinolyl ethyl ketone, picrate, and *iso*nitroso-, 96.
6-Methoxy-8-quinolyl methyl ketone, bromination of, 98.
β-6-Methoxyquinolyl(4)propionic acid, α-oximino-, and its ethyl ester, 89.
N^1-(6-Methoxy-8-quinolyl)-N^5-*iso*propyldiguanide hydrochloride, 1636.
N^1-(6-Methoxy-8-quinolyl)-N^4-*n*-propyl-N^5-*iso*propyl*iso*thiourea, and its hydrochloride, 1652.
6-Methoxyquinolyl(4)pyruvic acid, ethyl ester, 89.
5-Methoxysalicylic acid, methyl ester, β-primeveroside and its *O*-hexa-acetyl derivative, *O*-triacetyl-β-glucoside, and *O*-triacetyl-6′-*O*-trityl-β-glucoside, 2222.
4-Methoxystyrene, β:2-*di*nitro-5-hydroxy-, 5-acetyl derivative, 2226.
5-Methoxystyrene, β:2-*di*nitro-4-hydroxy, and its 4-acetyl derivative, 2226.
6-Methoxy-4-styrylquinoline *N*-oxide, and its picrate, 96.
1-Methoxy-5:6:7:8-tetrahydrophenanthridine, and its picrate, 1539.
3-Methoxy-5:6:9:10-tetramethyl-1:2-benzanthracene, 173.
5-Methoxytoluene, 2-hydroxy-, and its 2-benzyl derivative, 2307.
3-Methoxy-5:9:10-trimethyl-1:2-benzanthracene, 173.
6-Methoxy-4-vinylquinoline, picrate, 96.
2-Methoxy-*m*-5-xylenol, 2307.
Methyl alcohol, action of, on naphthalene, catalysed by alumina–silica catalysts, 804.
clathrate compound of, with quinol, 571.
Methyl 3-chloroallyl sulphide, 2181.
2-chloroethyl sulphilimine, 2179.
ether, methylation of naphthalene by, 1700.
reactions of, with benzene, toluene, and xylenes, 2154.
7-Methylacenaphthene, and its derivatives, 1397.
7-Methylacenaphthylene, and its derivatives, 1397.
***N*-Methylacetiminophenyl ether**, and its picrate, 1522.
***N*-Methylacetimino-*p*-tolyl ether**, and its hydrochloride, 1522.
3-Methylacetophenone, 2-amino-, and its acetyl derivative, and 2-nitro-, 1704.
4-Methylacetophenone phenylmethyl- and *p*-tolyl-hydrazones, 854.

4-Methylacetophenone, 2-amino-, 5-nitro-2-amino-, 3:5-*di*nitro-2-amino-, and their derivatives, 1704.
1-Methylacridine, 4-amino-, 1228.
2-Methylacridine, 5-amino-2-*tri*fluoro-, and its derivatives, and 5-chloro-2-*tri*fluoro-, 32.
4-Methylacridine, 5-amino-4-*tri*fluoro-, and its derivatives, 34.
9-Methylacridone, 2-*tri*fluoro-, 34.
4-Methylacridone, 4-*tri*fluoro-, 34.
5- and **8-Methylalloxazines**, 2133.
6- and **7-Methylalloxazines**, preparation of, 1313.
α- and **γ-Methylallyl halides**, etholysis of, 4.
7-Methylaminoalloxazine, and 7-nitroso-, 1930.
1-Methylaminoanthraquinone, 5-chloro-, 738.
2-Methylaminobenzamide, 4- and 5-nitro-, 366.
4-Methylamino*meso*benzanthrone, 1180.
6-Methylamino*meso*benzanthrone, 1749.
2-Methylaminobenzoic acid, 4- and 5-nitro-, and their methyl esters, 366.
4-Methylaminobutylbenzyl cyanide, 809.
2-Methylamino-4-carbethoxythiazole, 5-amino-, and its hydrochloride, and benzylidene derivative, 2030.
***m*-Methylamino-*N*-dimethylaniline**, and its dipicrate, 1929.
α-Methylamino-nitriles, reaction of, with carbon disulphide, 1619.
Methylaminophosphonic acid, diethyl ester, 702.
2(or 3)-Methyl-6-aminoquinoxaline, 2134.
2-Methylaminothiazole, 5-amino-, 2029.
***N*-Methyl-*N'*-*n*-amylbenzamidine**, preparation of, 1619.
5-Methyl-2-amylglyoxaline-4-carboxylic acid, ethyl ester, 1963.
Methyl *n*-amyl ketone, bromo-, 278.
5-Methyl-2-amyloxazole-4-carboxylic acid, 1963.
17(β)-Methylandrost-5-ene-3(β):17(α)-diol 3(β)-benzoate, 790.
6-*N*-Methylanilino*meso*benzanthrone, 1625.
Methyl 1-anilinoethyl ketone, and its semicarbazone, 275.
3-Methyl-2-β-anilinovinylbenziminazole methiodide, 1897.
6-Methyl-2-β-anilinovinylquinoline methiodide, 1897.
2-Methylanthraquinone, 3:5:6:7-*tetra*hydroxy-, and its derivatives, 991.
Methylation, biological, 1591.
2-Methyl-4-azabenziminazole, 6-bromo-, 1392.
2-Methyl-4-azaindole, 200.
2-Methyl-5-azaindole, 200.
Methyl 1-benzamidoethyl ketone 2:4-*di*nitrophenylhydrazone, 315.
1'-Methyl-1:2-benzanthracene, 3-hydroxy-, 3-benzoyl derivative, 173.
6-Methyl-3:4-benzfluorenone, 1233.
7-Methyl-3:4-benzfluorenone, 1234.
2-Methylbenzopteridine, 6-hydroxy-, and its acetyl derivative, 519.
2-Methylbenzoxazole hydrochloride, 2153.
[2-(3-Methylbenzoxazole)][3-(4-methyldihydro-β-quinindene)]-dimethincyanine iodide, 1897.
2-Methyl-5:6-benzquinoline, 4-amino-, and 4-chloro-, 1287.
2-Methyl-6:7-benzquinoline, 4-amino-, and 4-hydroxy-, 1288.
8-chloro-4-amino- and -4-hydroxy-, 1289.
2-Methyl-7:8-benzquinoline, 4-amino-, 1288.
1'- and 6-amino-, and 1'-nitro-, 1295.
4-Methyl-5:6-benzquinoline, 2-amino-, 1292.
4-Methyl-7:8-benzquinoline, 2-amino-, 1292.
2-Methyl-6:7-benzquinoline-3-carboxy-(2'-carboxy-3'-naphthyl)-amide, 4-hydroxy-, 1288.
5-Methylbenz-1-thia-2:3-diazole, and 7-nitro-, 1009.
[2-(3-Methylbenzthiazole)][3-(4-methyldihydro-β-quinindene)]-dimethincyanine iodide, 1898.
***p*-Methylbenzyl** methyl sulphide, *p*-amino-, hydrochloride, 1504.
Methylbenzylmalonic acid, amino-*p*-amino-, acetyl derivative, ethyl ester, and its derivatives, 87.
***p*-Methylbenzyl methyl sulphone**, *p*-amino-, hydrochloride, 1504.
Methyl 2-bromoethyl ketones, bromo-, and chloro-, 280.
Methyl 1-bromo-*n*-propyl ketone, 277.
Methyl 2-bromovinyl ketone, chloro-, 280.
2-Methylbut-3-ene, 2-chloro-, 530.
ω-Methyl-ω-*n*-butylacetophenone, and its 2:4-dinitrophenylhydrazone, 1743.
6-Methyl-2-*iso*butylcinchoninic acid, 108.
***N*¹-Methyl-*N*³-*n*-butyldicyandiamide**, 1650.
Methyl butyl ketones, bromo-, 278.
2-Methyl-2-*iso*butylquinoline, and its picrate, 108.
***S*-Methyl-*N'*-butyl*iso*thioureas**, *N*-cyano-, 1633.
2-Methylcarbamylphenylthioacetic acid, 84.
4-Methyl-5-(ω-carboxy-*n*-pentyl)iminazole-2-thione, 1553
4-Methyl-5-(ω-carboxy-*n*-pentyl)iminazol-2-one, 1553.
Methyl 2-chloroethyl ketone, bromo-, 280.
Methyl 2:2-*di*chloroethyl ketone, chloro-, 280.
Methyl 1:2:2-*tri*chloromethyl ketone, chloro-, 280.
Methyl 3-chloropropyl ketone, bromo-, 278.
Methyl 2-chlorovinyl ketones, bromo-, and chloro-, 280.
Methyl 1:2-*di*chlorovinyl ketone, chloro-, oxime and semicarbazone, 281.
2-Methylchroman-4-one, 7-hydroxy-, and its derivatives, 1611.
2-Methylcinchoninic acid, 6-bromo-, 108.
3-Methylcinnoline, 6-bromo-4-hydroxy-, 6-chloro-4-hydroxy-, 4-hydroxy-, and its acetyl derivative, 6-nitro-4-hydroxy-, and its acetyl derivative, and 8-nitro-4-hydroxy-, 357.
6-nitro-4-amino-, 8-nitro-4-amino-, and its acetyl derivative, 360.
7-Methylcinnoline, 4-chloro-8-nitro-, 4-hydroxy-, and its acetyl derivative, 8-nitro-4-amino- and -4-hydroxy-, and 6-nitro-4-hydroxy-, 1705.
8-Methylcinnoline, 4-amino-, 4-hydroxy-, nitro-4-amino-, and nitro-4-hydroxy-, 1706.
***Bz*-Methylcinnolines**, 4-hydroxy-, and 8-nitro-4-hydroxy-, preparation and reactions of, 1702.
3-Methylcoumaran, 6-hydroxy-, and its 6-benzyl derivative, 2258, 2259.
5-Methylcoumaran, 6-hydroxy-, and its derivatives, 2258.
β-3-Methylcoumaran-5-acrylic acid, β-6-hydroxy-, 6-acetyl derivative, 2259.
7-Methyl-β-coumaranone-2-carboxylic acid, ethyl ester, 1673.
3-Methylcoumarone-2-carboxylic acid, 6-hydroxy-, 6-acetyl derivative, 2258.
5'-Methylcoumarono-(2':3':3:4)-coumarin, 7-hydroxy-, and 5:7- and 7:8-*di*hydroxy-, and their acetates, 1673.
7'-Methylcoumarono-(2':3':3:4)-coumarin, 7-hydroxy-, and its derivatives, 1673.
1-Methyl-4-(cyanophenylmethylene)piperidine hydrochloride, 808.
Methyldi-(3-chloroallyl)amine, preparation of, 2182.
Methyldi-(2-chloroethyl)amine, compounds related to, 2174.
Methyldicyandiamide, preparation of, 1633.
Methyldi-(2-fluoroethyl)amine, 2176.
2-Methyl-5:10-dihydroarsacridine, 10-chloro-, 295.
3-Methyl-5:10-dihydroarsacridine, 10-chloro-, 298.
1'-Methyldihydro-1:2-benzanthracene, *di*hydroxy-, and its diacetate, 172.
3-Methyl-2:3-dihydrobenzthiazoles, 2-imino-, spectra of, absorption, ultra-violet, 1497.
20-Methyldihydrocholanthrene, *di*hydroxy-, and its diacetate, 173.
3'-Methyl-2':3'-dihydrofurano(4':5':6:7)coumarin, 2259.
3'-Methyl-2':3'-dihydrofurano(4':5':6:7)coumarin-3-carboxylic acid, 2259.
3-Methyl-5:6-dihydro-γ-pyrone-2-carboxylactone, 3-hydroxy-, and its bromo-derivative, 1298.
5-Methyl-5:11-dihydroquindoline, 11-imino-, 921.
6-Methyl-5:6-dihydrouracil, 5:5-*di*chloro-6-hydroxy-, action of hydrochloric acid on, 1988.
Methyl-3-dimethylaminomethylindoles, 708.
8-Methyl-2:6-dioxapyrrolizidine, 8-hydroxy-, and its derivatives, 1906.
3'-Methyldiphenyl sulphide, 2:6'-*di*nitro-, 2020.
4-Methyldiphenyl sulphide, 2:2'-*di*nitro-, 2020.
2:6:2'-*tri*nitro-, 2022.
5-Methyldiphenyl sulphide, 2:3:4'-*tri*nitro-, 2020.
4-Methyldiphenylamine, *tri*- and *tetra*-nitro-derivatives, 1993.
3'-Methyldiphenylamine-2-carboxylic acid, 3'-*tri*fluoro-, and its *p*-nitrobenzyl ester, 33.
4'-Methyldiphenylmethane, 2-amino-, 295.
5-Methyldiphenylmethane, 2-amino-, and its derivatives, 297.
5-Methyldiphenylmethane-2-arsonic acid, 298.
Methyldithiohydantoin, acetyl derivatives, 206.
Methylene-blue, absorption of, by cells of *Bacterium lactis aerogenes*, 2290.
Methylene compounds, reactive, addition of, to α-cyanoprene, 232.
4-Methylene-2-thiothiazolone, 4-hydroxy-, 1339.
***N*¹-Methyl-*N*³-ethyldicyandiamide**, 1650.
3-Methyl-2-ethylindole, preparation of, 277.

Methyl ethyl ketone, bromination of, 272.
Methyl ethyl ketone, amino-, α-bromopropionyl derivative, 1857.
oximino-, 1863.
Methyl ethyl ketoxime benzenesulphonate, 1518.
3′-Methyl-3-ethyloxathiacarbocyanine iodide, 690.
3-Methyl-4-ethylphenol, 6-amino-, 2146.
4-Methyl-5-ethylthiazole, 2-amino-, and its picrate, 277.
[2-(4-Methyl-3-ethylthiazole)][2-(3-ethylbenzselenazole)][αβ′-dimethin-2′-(3′-ethylbenzselenazole)]trimethincyanine *di*iodide, 1883.
[2-(4-Methyl-3-ethylthiazole)][2-(3-ethylbenzselenazole)]trimethincyanine iodide, 1887.
[2-(4-Methyl-3-ethylthiazole)][2-(3-ethylbenzthiazole)][αβ′-dimethin-2′-(3′-ethylbenzthiazole)]trimethincyanine *di*iodide, 1883.
[2-(4-Methyl-3-ethylthiazole)][2-(3-ethylbenzthiazole)]trimethincyanine iodide, 1887.
***S*-Methyl-*N*′-ethyl*iso*thiourea**, *N*-cyano-, 1633.
Methyl fluoroform. See Ethane, 1:1:1-*tri*fluoro-.
2-*N*-Methylformamidobenzoic acid, 4-nitro-, 366.
2-Methylfurano(2′:3′:5:6)chromone, 7-hydroxy-, 2264.
1-Methylglyoxaline, 5-amino-2-mercapto-, and its hydrochloride, 2029.
Methylgramines, 708.
6-Methylheptane, 1:6-*di*amino-, derivatives of, 231.
6-Methyl*cyclo*heptatrienone, 2-hydroxy-, 1051.
Methyl*cyclo*hexane, *tetradeca*fluoro-, spectrum of, infra-red absorption, 1432.
5-Methylhexane-1-carboxylic acid, 5-amino-, and 5-nitro-, and their derivatives, 231.
5-Methylhex-1-enyl cyanide, 5-nitro-, 231.
5-Methylhex-2-enyl cyanide, 5-nitro-, 230.
γ-(2-Methyl*cyclo*hex-1-enyl)butyric acid, synthesis of, 163.
5-Methylhexyl cyanide, 5-amino-, and its derivatives, and 5-nitro-, 230.
6-Methyl-2-*n*-hexylcinchoninic acid, 109.
6-Methyl-2-*n*-hexylquinoline, 109.
Methyl-1-hydrindanone, 164.
2-Methylimino-4-carbethoxy-3-acetylthiazoline, 5-amino-, 5-acetyl derivative, 2030.
2-Methylindole, 5-hydroxy-, and its 5-acetyl derivative, 1609.
5:6-*di*hydroxy-, and its 5:6-diacetyl derivative, 2225.
Methylindoles, and their derivatives, 707.
2-(7-Methyl-3-indolyl)ethane-1-carboxylic acid, 1-amino-1-cyano-, 1-acetyl derivative, ethyl ester, 709.
2-(Methyl-3-indolyl)ethane-1:1-dicarboxylic acids, 1-amino-, 1-acetyl derivatives, and their ethyl esters, 708.
9-Methyl-1:3:4-indotriazine, 2-amino-, and its salts, 2317.
1-Methylisatin, condensation of, with barbituric acid, 552.
anti- and *syn*-β-guanylhydrazones, and their salts and derivatives, 2316.
Methyl ketones, bromo-, preparation of, 278.
Methylmalonic acid, esters, 632.
Methyl β-mercapto*iso*butyl ketone, and its mercury mercaptide, 1684.
Methylmercuric iodide, *tri*fluoro-, 2190.
Methyl β-*p*-methylsulphonylphenylethyl ketone, chloro-, 1505.
2-Methylnaphthalene, derivatives, water-soluble, 182.
preparation of, 804.
2-Methyl-1:4-naphthaquinone-4-oxime-*O*-sulphonic acid, potassium salt, 185.
2-Methyl-1:4-naphthaquinone 4-carboxymethyl oxime, 185.
2-Methyl-1:4-naphthaquinone 4-β-diethylaminoethyl oxime hydrochloride, 185.
2-Methyl-1-naphthol, 4-chloroamino-, 4-acetyl derivative, 184.
2-Methyl-1-naphthoxyacetic acid, 4-amino-, and its 4-acetyl derivative, 184.
***N*-3-Methyl-1-naphthylglycine**, *N*-4-amino-, and its 4-acetyl derivative, ethyl ester, 184.
2-Methylnicotinamide, preparation of, 200.
Methyl 2-(2:4:6-*tri*nitrophenyl)ethyl sulphide, 1615.
Methyl 2-(2:4:6-*tri*nitrophenyl)ethyl sulphone, 1615.
5-Methylnona-2:7-diene, 5-nitro-1:9-*di*cyano-, 230.
5-Methylnonane, 5-nitro-1:9-*di*cyano-, 230.
5-Methylnonane-1:9-dicarboxylic acid, 5-nitro-, and its bisbenzylthiuronium salt, 232.
6-Methyl-2-*n*-nonylcinchoninic acid, 109.
5-Methyl-5-*n*-nonylhydantoin, 1388.
6-Methyl-2-*n*-nonylquinoline, 4-hydroxy-, 109.
ω-Methyl-ω-*n*-octylacetophenone, and its 2:4-dinitrophenylhydrazone, 1743.
4:4-(3′-Methyl*cyclo*pentamethylene)-3-methylthiazolidine-2-thione, 5-imino-, 1621.
4:4-(3′-Methyl*cyclo*pentamethylene)-3-methylthiazolid-5-one-2-thione, 1621.
***p*-Methylphenacyl-*N*-ethylaniline**, 855.
***p*-Methylphenacyl-*N*-methylaniline**, 855.
1- and 3-Methylphenanthridines, 9-amino-, 1540.
9-Methylphenanthridine, 2-amino-, 192.
6-amino-, and its hydrochloride, 194.
8-amino-, and 8-hydroxy-, and their hydrochlorides, 194.
Methylphosphonic acid, fluoro-, di-*sec.*-butyl ester, 702.
***O*-Methylpiscidic acid**, esters, 259.
2-Methylpropan-2-ol, 1:3-*di*nitro-, 56, 58.
Methyl*iso*propyldicyandiamide, 1633.
2-Methyl-1-propylene, 3-nitro-, 58.
***N*-(*N*-Methyl-*N*-*iso*propylguanyl)-*S*-methyl*iso*thiourea**, 1654.
***N*-Methyl-*N*-*iso*propylguanylthiourea**, 1654.
Methyl *n*-propyl ketone, bromo-, 277.
Methyl *n*- and *iso*-propyl ketones, bromination of, 276.
Methyl propyl ketones, bromo-, 278.
3-Methyl-4-*n*-propylphenol, 6-amino-, and 6-nitro-, methyl ether, 2146.
3-Methyl-4-*n*-propylphenoxyacetic acid, 2145.
***S*-Methyl-*N*′-propyl*iso*thioureas**, *N*-cyano-, 1633.
6-Methylpyridazine, 3-amino-, synthesis of, 2199.
3-mercapto-, 2200.
6-Methyl-3-pyridazone, sulphanilamides derived from, 2195.
2-Methyl-3-pyridazone, 4:5-*di*chloro-, 2194.
2-Methyl-3-pyridazone-6-carboxylic acid, and its methyl ester, and 5-chloro-, and 4:5-*di*chloro-, 2194.
6-Methyl-3-pyridazone-4-carboxylic acid, 2193.
4-Methylpyrimidine, derivatives, condensation of, with *p*-dimethylaminobenzaldehyde, 1715.
***N*-(6-Methyl-2-pyrimidyl)-*O*-ethyl*iso*urea**, *N*-4-hydroxy-, 585.
7-Methylquinazoline, 2:4-*di*hydroxy-, 1763.
1-Methyl-4-quinazolone, 6- and 7-nitro-, and their *p*-toluenesulphonates, 365, 366.
3-Methyl-4-quinazolone, 6- and 7-nitro-, preparation and decomposition of, 365.
5-Methyl*iso*quindoline, 7-nitro-, 920.
5-Methylquindolinium chloride, ψ-base from, 920.
chloride, 7-amino-, 11-amino-, and 7-nitro-, 920, 921.
iodide, 11-amino-, 921.
5-Methyl*iso*quinindoline, and 9-nitro-, 924.
11-Methylquinindoline, and its 6-acetyl derivative, 923.
5-Methylquinindolinium chloride, and 5-nitro-, 924.
5-(or 7)-Methylquinoline, 3-nitro-, 2027.
6-Methylquinoline, 3-amino-, 3-nitro-, and 3:5-*di*nitro-, 2027.
8-Methylquinoline, 3-nitro-, 2027.
6- and 8-Methylquinolines, 4-hydroxy-, 894.
6- and 8-Methylquinoline-3-carboxylic acids, 4-hydroxy-, and their ethyl esters, 894.
[2-(1-Methylquinoline)][3-(4-methyldihydro-β-quinindene)]cyanine iodide, 1897.
[2- and 4-(1-Methylquinoline)][3-(4-methyldihydro-β-quinindene)]dimethincyanine iodides, 1897.
1-Methyl-4-quinolone, 6-nitro-, 1709.
3-Methylquinoxaline, 2-amino-, and 2-chloro-, 2133.
2-chloro-, and 2-hydroxy-3-chloro-, 522.
5-Methylquinoxaline, 2-amino-, 7-amino-, 2-chloro-, and 2-hydroxy-, 2133, 2134.
6-Methylquinoxaline, 2-amino-, 2-chloro-, and 2-hydroxy-, 1312, 1313.
7-amino-, 2134.
7-Methylquinoxaline, 2-amino-2-chloro-, and 2-hydroxy-, 1312, 1313.
5-amino-, and its monohydrate, 2134.
8-Methylquinoxaline, 2-amino-, 2133.
5-Methylquinoxaline-3-carboxylic acid, 2-hydroxy-, 2134.
6- and 7-Methylquinoxaline-3-carboxylic acids, 1313.
***O*-Methylrepandine** *di*methiodide, 2172.
***O*-Methylrepandinemethine** *di*methiodide, 2172.
2-Methyl ribitol, 1382.
Methyl-D-ribofuranoside, 2035.
***p*-Methylstilbene**, photochemical reaction of, with phenanthraquinone, 2127.
4-Methylstilbene, 4-bromo-, 227.
α-Methylstyrene, Prins reaction with, 89.

β-Methylstyrene, 2:β-*di*nitro-5-hydroxy-, 5-acetyl derivative, 1609.
β:2-*di*nitro-4:5-*di*hydroxy-, 4:5-diacetyl derivative, 2225.
Methylsuccinic acid, esters, 666.
6-Methylsulphinylnicotinamide, 1943.
Methylsulphonyl-. See also Methanesulphonyl-.
p-Methylsulphonylacetophenone, 603.
p-Methylsulphonylbenzamidine, hydrochloride, anti-bacterial activity of, effect of homologation on, 1501.
preparation of, 306.
p-Methylsulphonylbenzenesulphonamide, 604.
p-Methylsulphonylbenzoic acid, methyl ester, 1506.
p-Methylsulphonylbenzophenone, 603.
p-Methylsulphonylbenzoylacetic acid, ethyl ester, 1506.
p-Methylsulphonylbenzthioamide, 1507.
p-Methylsulphonylbenzylamine hydrochloride, antibacterial activity of, effect of homologation on, 1501.
6-Methylsulphonylnicotinamide, 1943.
6-Methylsulphonylnicotinamidine, salts, 1943.
p-Methylsulphonylphenylacetamide, 1504.
p-Methylsulphonylphenylacetamidine, hydrochloride, 1505.
p-Methylsulphonylphenylacetic acid, and its ethyl ester, 1504.
p-Methylsulphonylphenylacetonitrile, 1504.
β-p-Methylsulphonylphenylalanine, 1506.
γ-p-Methylsulphonylphenyl-*n*-butylamine hydrochloride, 1506.
γ-p-Methylsulphonylphenyl-*n*-butyramide, 1505.
γ-p-Methylsulphonylphenyl-*n*-butyramidine benzoate and hydrochloride, 1505.
γ-p-Methylsulphonylphenyl-*n*-butyronitrile, 1505.
4-β-p-Methylsulphonylphenylethyl-2-aminothiazole, hydrochloride, 1505.
2-p-Methylsulphonylphenyl-6-methylpyrimidine, 4-chloro-, and 4-hydroxy-, 1507.
2-p-Methylsulphonylphenyl-4-methylthiazole-5-carboxylic acid, ethyl ester, 1507.
β-p-Methylsulphonylphenylpropionamide, 1505.
β-p-Methylsulphonylphenylpropionamidine benzoate and hydrochloride, 1505.
β-p-Methylsulphonylphenylpropionitrile, 1505.
γ-p-Methylsulphonylphenyl-*n*-propylamine hydrochloride, 1505.
p-Methylsulphonylphenylthioacetmorpholide, 1504.
2-Methylsulphonylpyridine, 5-amino-, and 5-nitro-, 1944.
5-cyano-, 1942.
p-Methylsulphonylthioanisole, 605.
1-Methyl-5:6:7:8-tetrahydrophenanthridine, 9-amino-, 1540.
2(or 4)-Methyl-5:6:7:8-tetrahydrophenanthridine, and its picrate, 1539.
3-Methyl-5:6:7:8-tetrahydrophenanthridine, 9-amino-, 1540.
3-Methylthienylsulphonic acid, amide and chloride of, 771.
p-Methylthioacetophenone, 603.
p-Methylthiobenzenesulphinic acid, 604.
p-Methylthiobenzenesulphonamide, 604.
p-Methylthiobenzenesulphonyl chloride, 604.
4-Methylthio-6-dimethyldihydro-1:3:5-triazine, 2-amino-, 1655.
2-Methylthioethanethiol, 1895.
2-Methylthioglyoxaline, 4-mercapto-, methiodide, 206.
2-Methylthio-4-*n*-hexylthiazole, 5-amino-, 5-acetyl derivative, 2032.
6-Methylthionicotinamide, 1943.
6-Methylthionicotinamidine, salts, 1943.
2-p-Methylthiophenylguanidino-6-methylpyrimidine, 4-hydroxy-, 579.
N^1-p-Methylthiophenyl-N^5-*iso*propyldiguanide hydrochloride, 1635.
2-Methylthiopyridine, 5-amino-, and 5-nitro-, 1944.
5-cyano-, 1942.
2-Methylthiothiazole, 5-amino-, 205.
2-2′-Methylthiovinylbenzthiazole methiodide, 689.
α-Methyltridecylic acid, α-amino-, 1388.
2-Methyltrimethylene sulphate, 2-nitro-2-chloro- and -2-hydroxy-, 1904.
Methyltryptophans, and their derivatives, 708.
5-Methyl-5-*n*-undecylhydantoin, 1388.
α-Methylundecylic acid, α-amino-, 1388.
4-Methyluracil, 5-nitro-, piperidine salt, 1131.
6-Methyluracil, 5:6-*di*chloro-, 1988.
5-Methylureido-2-mercapto-1-methylglyoxaline, and its picrate, 2029.
Methyl vinyl ketone, chloro-, 281.
Methylxanthines, dissociation constants of, 765.
Mills–Nixon effect, 730.
Mineral, new, zeolitic, 127, 133.
Molecular association, viscosity and, 1345, 1349.
asymmetry based on isotopic differentiation of hydrogen, 1085.
compounds. See under Compounds.
rotation. See under Rotation.
structure, correlation of, with vibrational absorption spectra, 328.
Mordenite, synthesis and reactions of, 2158.
Morindin, hydrolysis and methylation of, 567.
β-Morindin, 566.
Morindone, derivatives of, and its dyeing properties, 567, 568.
4-Morpholinobutylbenzyl cyanide, and its picrate, 809.
2-Morpholino-4-(4-dimethylaminostyryl)-6-methylpyrimidine, 2151.
2-Morpholinoethylbenzyl cyanide, 809.
2-Morpholino-5-methylhexyl cyanide, 5-nitro-, 231.
γ-Morpholino-α-phenylbutyric acid, ethyl ester, hydrochloride, 809.
ε-Morpholino-α-phenylhexoic acid, ethyl ester, 809.
Morpholinophosphonic acid, diethyl ester, 702.
Mycobacterium tuberculosis, human, polysaccharides from, 1211, 1220.

N.

Naphthalene, diamidino-derivatives from, 261.
methylation of, with dimethyl ether, 1700.
reaction of, with methyl alcohol, catalysed by alumina–silica catalysts, 804.
with styrene, 1397.
substitution in, 729.
synthesis of *as*-hydrocarbons from, 1395.
Naphthalene, 1-halogeno-derivatives, 100.
1:5-*di*hydroxy-, bromination of, and its methyl ethers, 1283.
1:4-*di*nitro-, preparation of, 1513.
Naphthalene series, *anti*-diazosulphonates of, 1183.
Naphthalene-1:1′-azo-2′-naphthol, 4-chloro-, 1186.
Naphthalene-1-diazosulphonic acid, 4-chloro- and 4-nitro-, sodium salts, 1186.
Naphthalene-2-diazosulphonic acid, sodium salt, 1186.
α-Naphthaquinone, photo-dimerisation of, 2128.
1:4-Naphthaquinone, 2:6-*di*bromo-5-hydroxy-, preparation of, 1284.
1:8-Naphthasultam, action of ethereal diazomethane on, 606.
***peri*Naphthindane-7:8:9-trione**, photochemical reaction of, with stilbene, 2128.
***peri*Naphthindenone**, *di*hydroxy-, preparation of, 182.
2-Naphthoic acid, 3-amino-, 3-acetyl derivative, ethyl ester, 1288.
1-bromo-, ethyl ester, 1233.
1-hydroxy-, esters, and naphthol-blue dyes therefrom, 309.
Naphthol-blue dyes from 1-hydroxy-2-naphthoates, 309.
β-Naphthol-1-sulphonic acid, diazosulphonates from, phthalazine reaction with, 206, 281, 597, 1026, 1249.
Naphthoylbenzoic acids, chloro-, and their acetoxylactones, 1758.
***N*-β-Naphthoyl-*p*-toluenesulphonamide**, 111.
α-Naphthyl group, parachor and refractivity of, 654.
9-(1′- and -2′-Naphthyl)*iso*alloxazines, 223.
1-Naphthylamine, 4-chloro-, and 2- and 4-nitro-, preparation of, 1183.
α- and β-**Naphthylamino*meso*benzanthrones**, 1749.
2-α-Naphthylaminobenzoic acid, 2-5′-nitro-, 1291.
2-β-Naphthylaminobenzoic acid, 4-chloro-, 126.
4-(1′-Naphthylamino)diphenyl, 3-amino-, and 3-nitro-, 222.
2-β-Naphthylbutane, and its derivatives, 1397.
α- and β-**Naphthyldicyandiamides**, 1634.
α-Naphthyl ethynyl ketone, 2038.
***N*-α-Naphthylmethyl-*p*-toluidine**, 298.
1-(1-Naphthyl)-2-(2-naphthyl)ethylene, **1602**,
α-1-Naphthylpropionamide, 1676.
N^1-2-Naphthyl-N^5-*iso*propyldiguanide, N^1-6-bromo-, 1635.
1-Naphthylpyridine picrate, 2219.
2-(2′-Naphthyl)-Δ^2-pyrroline, and its picrate, 187.
Neocyanines with dissimilar nuclei, 1872.

Neodymium salts, separation of, from cerium salts, by ion exchange, 1272.
Nickel, catalytic, Raney, use of, as reducing agent, 1716.
Nicotinamide, 6-chloro-, 1942.
6-mercapto-, 1943.
Nicotinamidine, 6-mercapto-, salts, 1943.
Nitrates. See under Nitrogen.
Nitrites. See under Nitrogen.
*poly***Nitro-compounds,** aromatic, reactions of, with alkaline sulphides, 2017.
monoreduction of, 1275.
Nitrogen, solubility and diffusion of, in polystyrene, 1541.
Nitrogen *tetr*oxide, addition of, to olefins, 52.
oxidation of cellulose by, 1135.
Nitrates, reduction of, to nitrites by coliform bacteria, 824, 833, 841.
Nitrites, utilisation of, by coliform bacteria, 824, 833, 841.
Nitrogen–hydrogen–oxygen linking, 874.
Nitrogen–nitrogen linkings, heat of formation of, 1187.
Nitro-groups, replacement of diazonium groups by, 1512.
Nitro-hydrocarbons, *p*-reactivity of, 351.
Nitro-paraffins, addition of, to α-cyanoprene, 227.
co-ordinate link in, and refractivity, 1833.
Nitrosyl chloride, action of, on metals and their chlorides, 1952.
Nona-2:7-diene-5:5-dicarboxylic acid, 1:9-*di*cyano-, ethyl ester, 233.
Nonane-5-carboxylic acid, 1:5:9-*tri*cyano-, ethyl ester, 234.
Nonane-5:5-dicarboxylic acid, 1:9-*di*cyano-, ethyl ester, 233.
2-*n*-Nonylcinchoninic acid, and 6-bromo-, 109.
2-*n*-Nonylquinoline, and 6-bromo-, and their picrates, and 6-bromo-4-hydroxy-, 109.
Norpethidine, and its carbonate, 561.

O.

Obituary notices :—
Francis William Aston, 1468.
Edward Charles Cyril Baly, 1721.
Marmaduke Barrowcliff, 1475.
George Thomas Byrne, 253.
Bernard Shirley Dyer, 896.
Percy Faraday Frankland, 1996.
John Masson Gulland, 1476.
Ernald George Justinian Hartley, 899.
Sir Philip Joseph Hartog, 901.
David Hooper, 253.
Victor Lefebure, 394.
Dorothy Jordan Lloyd, 1727.
George Newbery, 255.
Edgar Philip Perman, 256.
Frederick Maurice Rowe, 2323.
Alfred Walter Stewart, 396.
Frank Clifford Whitmore, 1090.
Octane, 1:6-*di*amino-, and its dipicrate, 231.
Octan-7-one-1-carboxylic acid, 6-amino-, and its hydrochloride, and 6-chloro-, and its ethyl ester, 1553.
Octenes, intensity of double-bond valence vibration in, 1456.
***n*-Octyl** cyanide, 1-amino-, hydrochloride, 2031.
β-*n*-Octylsuccinic acid, α-amino-, 1389.
***p*-*n*-Octylsulphonylbenzylammonium** chloride, 382.
***p*-*n*-Octylsulphonylphenyl** cyanide, 383.
Œstrogens, synthetic, of triphenylethylene series, 150.
Olefins, addition to, of dinitrogen tetroxide, 52.
formation of, from *n*-alkyl bromides, kinetics of, 2055.
from *tert.*-alkyl bromides, kinetics of, 2065.
from alkyldimethylsulphonium salts, kinetics of, 2072, 2077, 2084, 2094.
from *n*-amyl, *sec.*-butyl, and *iso*propyl bromides, kinetics of, 2058.
from *tert.*-amyl- and *tert.*-butyl-sulphonium salts, 2038.
solvent effects in, 2043.
temperature effects in, 2049.
α-methylenic activity in, 89.
reaction of, with organic per-acids, 1331.
Oleic acid, methyl ester, autoxidation of, 2275.
catalytic thermal oxidation of, 343.
Optical inversion, Walden's, steroids and, 1032, 1043.
Organic compounds, thermochemical evaluation of bond strengths in, 1161.
Osmium *tetr*oxide, oxidation with, of carcinogenic hydrocarbons, 170.
8-Oxa-3-aza*bicyclo*[3:2:1]octane, and its derivatives, 157.
Oxalic acid, lead salt, thermal decomposition of, 1898.
Oxazoles, 1960.
Oxazoles, 4-cyano-, synthesis of, 1969.
Oxidation of ethenoid fatty acids and their esters, 343.
with chromic acid, 1666.
Oxides, properties of, at high temperatures, 1729.
Oxy-acids, esters, co-ordinate link in, and refractivity, 1833.
Oxycelluloses, produced by oxidation of cellulose by dinitrogen tetroxide, 1135.
Ozone, structure of, 1299.

P.

Palm oil, glycerides of, and their configuration, 722.
Paludrine, benziminazole analogues of, 1366.
Parachor of acetals, 616.
of acetylenic compounds, 674.
of aliphatic acids and alcohols, 1814.
of aliphatic carboxylic esters, 624.
of aliphatic disulphides, sulphides, and thiols, 1820.
of *n*-alkylbenzenes, 607.
of amines, 1825.
of compounds with 3- and 4-membered carbon rings, 1804.
of compounds with 5- and 6-membered carbon rings, 1809.
of cyanides, 674.
of esters of oxy-acids and of nitro-paraffins, 1833.
of ethers, 616.
of ethylenic compounds, 658.
of halogens, 644.
of ketones, 610.
of α-naphthyl and phenyl groups, 654.
Patulin, synthesis of, 1295.
Pectic substances, 2311.
Pectin, sugar-beet, araban component of, 2311.
Pedler Lecture, 386.
Penicillenic acid, analogues of, 1060.
Penicillic acid, compounds related to, 1508.
synthesis of, 1508.
Penicillin, synthesis of, experiments on, 1964.
***n*-Pentadecane-8-carboxylic acid.** See α-*n*-Heptylpelargonic acid.
***cyclo*Pentamethylenedicyandiamide,** 1633.
***NN-cyclo*Pentamethyleneguanidine,** sulphate, 1643.
Pentamethyleneimine, 2-imino-, 1522.
4:4-*cyclo*Pentamethylene-3-methylthiazolidine-2-thione, 5-imino-, 1621.
4:4-*cyclo*Pentamethylene-3-methylthiazolid-5-one-2-thione, 1621.
1:2:2:6:6-Pentamethyl-4-ethynylpiperidine, 4-hydroxy-, and its 4-acetyl derivative, perchlorate, 808.
***n*-Pentane,** 1-nitro-, preparation and physical properties of, 1847.
Pentan-2-ol, 1-amino-, and its 1-benzoyl derivative, 1909.
Pentan-2-one, 1-amino-, 1-benzoyl derivative, 1909.
*tetra*bromo-, 277.
***cyclo*Pentanone** oxime benzenesulphonate, 1518.
6:12:18:24:30-Pentaoxa-3:9:15:21:27:33-hexathiapentatriacontane, 1:35-*di*chloro-, and its derivatives, 44.
3:6:9:12:15-Pentathiaheptadecane, 1:7-*di*chloro-, 46.
Pent-3-ene, 1-nitro-2-hydroxy-, 2-acetyl derivatives, and 1-nitro-2-3:5-*di*nitrohydroxy-, 3:5-dibenzoyl derivative, 1908.
Pent-2-ene-5:5-dicarboxylic acid, 1-cyano-, ethyl ester, 233.
Pent-3-en-2-ol, 1-nitro-, derivatives, 1907.
5:6-*cyclo*Pentenopyrimidine, 2-cyanoamino-4-hydroxy-, 578.
***cyclo*Pentindene,** 974.
***cyclo*Pentyl** ethyl and methyl ethers, 1811.
Peracetic acid, preparation of, and its reaction with β-di*iso*butylene, 286.
with di*iso*butylene, 1330.
Per-acids, organic, reaction of, with α-di*iso*butylene, 1328.
with β-di*iso*butylene, 284.
with olefins, 1331.
Perbenzoic acid, reaction of, with di*iso*butylene, 1329.
Performic acid, reaction of, with di*iso*butylene, 1329.
Periodates. See under Iodine.
Periodic system of the elements, 318.

Peroxides, bond energies in, 331.
bond strengths in, 403.
preparation of, 2216.
Persulphates. See under Sulphur.
Pethidine, homologues of, and their pharmacology, 559.
Pfitzinger reactions in synthesis of quinoline derivatives, 106.
Phenacyl-*N*-alkylarylamines, stability and reactions of, 847.
Phenacylarylamines, conversion of, into indoles, 847, 858.
isomerisation and indolisation of, 858.
Phenacyl-*p*-chloroaniline, 869.
Phenacyl-3:4-dimethylaniline, 869.
Phenacyl-*p*-ethylaniline, 869.
1-Phenacyl-2(or 3)-phenyl-5-ethylindole, 870.
1-Phenacyl-2(or 3)-phenyl-5-methylindole, 869.
Phenanthraquinone, photochemical reactions of, with ethylenes, 2126.
Phenanthridine, 2:7:9-*tri*amino-, and 9-chloro-2:7-*di*nitro-, 1292.
Phenanthridine series, syntheses in, 1284.
Phenanthridinium salts, trypanocidal properties of, 188.
Phenanthro(9′:10′:2:3)-5-azaquinoxaline, 7-bromo-, 1391.
***p*-Phenanthroline**, 1-amino-, 1290.
Phenazine, 1:3-*di*hydroxy-, and its 1:3-diacetyl derivative, 2318.
Phenols, oxidation of, by persulphates, 2303.
oxidation products of, 116.
Phenolsulphonic acids, 2-amino-, nuclear-substituted, preparation of, 212.
Phenol-2-sulphonic acid, 3:4- and 5:4-*di*chloro-, and their potassium salts, 213, 214.
Phenol-6-sulphonic acid, 2:3:4-*tri*chloro-, and its sodium salt, 3:4- and 4:5-*di*chloro-2-amino-, and 3:4-*di*chloro-2-nitro-, and its sodium salt, 214.
***N*-Phenoxyacetyl-*p*-toluenesulphonamide**, 111.
"α"-7-Phenoxycholesterol, and its esters, 1803.
4-Phenoxycinnoline, 8-chloro-, and 8-nitro-, 1705.
6-nitro-, 359.
4-Phenoxy-3-methylcinnoline, 358.
4-Phenoxy-3-methylcinnoline, 6- and 8-nitro-, 358.
4-Phenoxy-7-methylcinnoline, and 8-nitro-, 1705.
4-Phenoxy-8-methylcinnoline, and nitro-, 1706.
4-Phenoxyquinazoline, 6- and 7-nitro-, 364.
2-Phenoxyquinoline, 6-nitro-, 1708.
4-Phenoxyquinoline, 6- and 8-nitro-, 1708.
Phenyl alkyl sulphides, preparation and properties of, 1822.
n-amyl and hexyl sulphides, 1823.
aryl sulphides and sulphoxides, preparation of, with phenylmagnesium bromide, 528.
4-nitro-1-naphthyl sulphide, 2:4-*di*nitro-, 2022.
2:4-*di*nitro-1-naphthyl sulphides, 2- and 4-nitro-, 2022.
4:5-*di*nitro-1-naphthyl sulphide, 2022.
n-propyl ether, *p*-bromo-, preparation of, 153.
2-thienyl sulphide and sulphoxide, 526.
2-thienyl sulphide, *p*-nitro-, 527.
7-Phenylacenaphthene, and its trinitrobenzene derivative, 1397.
7-Phenylacenaphthylene, and its derivatives, 1397.
2-Phenylacetamidodiphenyl, 2-*p*-nitro-, 196.
Phenylacetic acid, halogen derivatives, preparation of, 1251.
Phenylacetic acids from 2-nitro-derivatives of vanillin, *iso*vanillin, and veratraldehyde, 376.
Phenylacetic acids, bromo-, and chloro-, and their derivatives, 1254.
Phenylaceto-β-naphthalide, and *o*- and *p*-bromo-, 1255.
Phenylacetone, 2-nitro-4-amino-, oxime, 1718.
2:4-*di*nitro-, derivatives of, 1717.
***p*-Phenylacetophenone** phenylethyl-, phenylmethyl-, and *p*-tolyl-hydrazones, 854.
Phenylacetylmethylcarbinol *p*-nitrobenzoate, 1676.
***N*-Phenylacetyl-*p*-toluenesulphonamide**, 111.
β-Phenylacrylamide, α-amino-, and its isomeride, 1063.
6- or 7-Phenylalloxazine, 222.
α-Phenylallyl esters, bimolecular isomerisation in, 1.
4-Phenyl-1-allylpiperidine-4-carboxylic acid, ethyl ester, and its hydrochloride, 561.
Phenylammonium benzenesulphonate, *p*-bromo-, 1525.
methanesulphonate, 1522.
4-Phenyl-1-*n*-amylpiperidine-4-carboxylic acid, ethyl ester, and its hydrochloride, 561.
1-Phenyl-1-*p*-anisyl-2-*p*-ethoxyphenylethylene, 2-bromo-, 155.
Phenylarsonic acid, *p*-thiocyanato-, 375.
Phenyl aryl sulphones, preparation of, with phenylmagnesium bromide, 528.
***N*-Phenylbenziminо-5:7-*di*chloro-8-quinolyl ether**, 1605.
***N*-Phenylbenziminoethyl ether**, 1523.
***N*-Phenylbenzimino-β-naphthyl ether**, 1523.
***N*-Phenylbenziminophenyl ether**, 1523.
***N*-Phenylbenzimino-8-quinolyl ether**, 1604.
N-*o*-chloro-, 1605.
9-Phenyl-7:8-benzo*iso*alloxazine, 222.
2-Phenyl-5:6-benz-1:3-oxazine, 5:2′-*di*nitro-6′-hydroxy-, and its acetyl derivative, 1609.
***N*-Phenyl-*N*′-benzylbenzamidine**, and its picrate, 519.
β-Phenyl-*S*-benzylcysteine, 1063.
2-Phenyl-4-benzylideneoxazol-5-one, 315.
Phenyl α-bromo-*p*-methylbenzyl ketone, 866.
γ-Phenylbutaldehyde, γ-*o*-hydroxy-, and its 2:4-dinitrophenylhydrazone, 1577.
3-Phenylbutane-1:3-diol, derivatives of, 93.
3-Phenylbutan-3-ol, 1-chloro-, 93.
Phenyl-*n*-butylcarbamic acid, ethyl and methyl esters, 878.
***N*¹-Phenyl-*N*⁵-*n*-butyldiguanide**, *N*¹-*p*-chloro-, 1643.
2-*N*¹-Phenyl-*N*³-*n*-butylguanidino-*N*⁵-4-β-diethylaminoethylamino-6-methylpyrimidine, 2-*N*¹-*p*-chloro-, and its dihydrochloride, 593.
***N*-Phenyl-*N*′-*n*-butylguanylthiourea**, *N*-*p*-chloro-, 1642.
4-Phenyl-1-*sec.*-butylpiperidine-4-carboxylic acid, ethyl ester, and its hydrochloride, 561.
3-Phenyl-3-*iso*butyrylpropanecarboxylic acid, 1744.
3-Phenyl-3-*iso*butyrylpropyl cyanide, 1744.
Phenylcarbamic acid, *o*-bromo-, and 2:5-*di*chloro-, ethyl esters, 881.
4-chloro-2-nitro-, ethyl ester, 878.
2-Phenylcarbamylphenylthioacetic acid, and its *N*-phenylimide, 85.
***N*-Phenyl-2:4-*di*chlorobenzamidine**, and its salts, 306.
1-Phenyl-1-*p*-chlorophenyl-2-*p*-acetylphenylethylene, and its oxime, 1080.
2-Phenyl-2-*p*-chlorophenyl-1-*p*-nitrophenylethylene, 1-bromo-, 1081.
3-Phenylcoumarin, 4:7-*di*hydroxy-, and its derivatives, 175.
β-Phenylcysteine hydrochloride, 1065.
synthesis of, 1060.
β-Phenyl-α-deuteropropionic acid, preparation of, and attempted asymmetric synthesis, 1086.
Phenyldicyandiamide, *p*-chloro-, and *p*-iodo-, 1634.
p-fluoro-, 1634.
2-Phenyl-1:1-di-*p*-ethoxyphenylethylene, 2-bromo-, 155.
2-Phenyl-5-3′:4′-diethoxyphenyl-4-methyloxazole, 890.
***N*′-Phenyl-*N*-(4-2′-diethylaminoethylamino-6-methyl-5-ethyl-2-pyrimidyl)formamidine**, *N*′-*p*-chloro-, 1716.
***N*′-Phenyl-*N*-(4-2′-diethylaminoethylamino-6-methyl-2-pyrimidyl)formamidine**, *N*′-*p*-chloro-, 1716.
***N*-Phenyl-*N*′*N*′-di-(2-fluoroethyl)urea**, 2176.
3-Phenyl-3:4-dihydrophthalazine, 1:4-*di*hydroxy-3-(2′-chloro-5′-nitro-), 209.
3-Phenyl-3:4-dihydrophthalazine-4-acetic acid, 1-hydroxy-, and its derivatives, 1250.
1-hydroxy-3-(2′:4′6′-*tri*bromo-), and its derivatives, 598.
1-hydroxy-3-2′-chloro-, and its derivatives, 1027.
1-hydroxy-3-3′-chloro-, and its derivatives, 600.
1-hydroxy-3-4′-chloro-, 601.
1-hydroxy-3-(2′-chloro-5′-amino-), 308.
1-hydroxy-3-(2′-chloro-5′-nitro-), and its derivatives, 207.
3-Phenyl-3:4-dihydrophthalazine-1-sulphonic-4-acetic acid, 3-(2′:4′:6-*tri*bromo-), sodium hydrogen salt, 598.
3-2′-chloro-, sodium hydrogen salt, 1027.
3-3′-chloro-, sodium hydrogen salt, 600.
3-4′-chloro-, sodium hydrogen salt, 601.
3-(2′-chloro-5′-nitro-), sodium hydrogen salt, 207.
Phenyl 3:4-dimethoxybenzyl ketone, 2:4-*di*hydroxy-, 175.
***N*′-Phenyl-*N*-(4:6-dimethoxy-2-pyridyl)formamidine**, *N*′-*p*-chloro-, 1716.
2-Phenyl-4-*p*-dimethylaminobenzylidene-5-oxazolone, 87.
α-Phenyl-α-(2-dimethylaminoethyl)butyrolactone, and its hydrochloride, 808.

4-Phenyl-3:3-dimethylbutanecarboxylic acid, and its *S*-benzylthiouronium salt, 1743.
lactone, 1745.
N^1-Phenyl-N^3:N^5-dimethyldiguanide, N^1-*p*-chloro-, and its hydrochloride, 1641.
N^1-Phenyl-N^4:N^5-dimethyldiguanide, N^1-*p*-chloro-, and its hydrochloride, 1651.
N^1-Phenyl-N^5:N^5-dimethyldiguanide, and its hydrochloride, and N^1-*p*-chloro-, 1644.
N^1-Phenyl-N^5:N^5-dimethyl-N^2-ethyldiguanide, N^1-*p*-chloro-, acetate, 1645.
***N*-Phenyl-*N'*-(*NN*-dimethylguanyl)-*S*-ethyl*iso*thiourea,** *N*-*p*-chloro-, 1642.
***N*-Phenyl-*N'*-(*NN*-dimethylguanyl)thiourea,** and *N*-*p*-chloro-, 1642.
2-Phenyl-4:5-dimethyliminazole, 734.
2-Phenyl-4:5(or 5:6)-dimethylindole, 870.
1-Phenyl-2:4-dimethylnaphthalene, 1-2-amino-, and its acetyl derivative, and 1-2-nitro-, 1139.
N^1-Phenyl-N^3:N^5-dimethyl-N^5-*iso*propyldiguanide, N^1-*p*-chloro-, and its acetate, 1641.
N^1-Phenyl-N^3:N^5-di*iso*propyldiguanide, N^1-*p*-chloro-, hydrochloride, 1644.
N^1-Phenyl-N^4:N^5-di*iso*propyldiguanide, N^1-*p*-chloro-, and its hydrochloride, 1651.
2'-Phenyl-2:6'-diquinolyl, 2'-*p*-amino-, and -nitro-, 2011.
Phenyldithiobiuret, *p*-chloro-, 1653.
***o*-Phenylene *di*cyanide, 3:6-*di*hydroxy-, 3:6-diacetyl derivative,** 305.
***p*-Phenylenebis*di*chloroarsine,** 2212.
Phenyl *p*-ethoxybenzyl ketone, preparation of, 152.
2-Phenyl-1-ethoxyphenyl-1-*p*-*n*-propoxyphenylethylene, 2-bromo-, 155.
1-Phenylethyl alcohol, 2:2:2-*tri*chloro-1-*p*-amino-, and its 1-*p*-acetyl derivative, 1459.
2-(2':6'-*di*nitro-4'-amino-), and its diacetyl derivative, 1277.
2-Phenylethyl alkyl and amyl sulphides, 2-(2:4:6-*tri*nitro-), 1612.
chloride, 2-(2:4:6-*tri*nitro-), 1614.
N^1-Phenyl-N^3-ethyl-N^5-*n*-butyldiguanide, N^1-*p*-chloro-, hydrochloride, 1645.
N^1-Phenyl-N^5-ethyl-N^2-*n*- and -*iso*-butyldiguanides, N^1-*p*-chloro-, hydrochlorides, 1644.
4-Phenyl-1-ethyldecahydroquinoline, and its picrate, 2016.
4-Phenyl-1-ethyldecahydroquinoline, 4-*p*-hydroxy-, hydrobromide, 2017.
N^1-Phenyl-N^3-ethyldicyandiamide, N^1-*p*-chloro-, and N^1-*p*-iodo-, 1639, 1640.
N^1-Phenyl-N^5-ethyldiguanide, N^1-*p*-chloro-, 1643.
1-Phenylethyldimethylsulphonium salts, olefin formation from, 2077.
2-Phenylethyldimethylsulphonium salts, olefin formation from, 2072.
2-N^1-Phenyl-N^2-ethylguanidino-N^3-4-β-diethylaminoethylamino-6-methylpyrimidine, 2-N^1-*p*-chloro-, 593.
***N*-Phenyl-*N'*-ethylguanylthiourea,** *N*-*p*-chloro-, 1642.
3-Phenyl-3-ethylpentanecarboxylic acid, and its *S*-benzylthiouronium salt, 1744.
4-Phenyl-1-ethylpiperidine-4-carboxylic acid, ethyl ester, 561.
N^1-Phenyl-N^3-ethyl-N^5-*iso*propyldiguanide, N^1-*p*-bromo-, hydrochloride, 1645.
N^1-*p*-chloro-, and its hydrochloride, 1641, 1644.
N^1-Phenyl-N^4-ethyl-N^5-*iso*propyldiguanide, N^1-*p*-chloro-, and its hydrochloride, 1652.
N^1-Phenyl-N^5-ethyl-N^2-*n*- and -*iso*-propyldiguanides, N^1-*p*-chloro-, hydrochlorides, 1644.
2-Phenylethylpyridinium salts, 2-(2:4:6-*tri*nitro-), 1614.
2-Phenylethylquinolinium chloride, 2-(2:4:6-*tri*nitro-), 1615.
3-Phenyl-3-ethylundecanecarboxylic acid, 1745.
Phenylglycine, *m*-bromo-, and its ethyl ester, and nitroso-, 2309.
N-nitroso-, and its benzyl ester, dipole moments of, 2269.
Phenyl group, parachor and refractivity of, 654.
Phenylguanidine, *p*-chloro-, 590.
2-Phenylguanidine-4-amino-6-methylpyrimidines, 4-substituted, 580.
4-Phenylguanidino-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine, 4-*p*-chloro-, 591.
2-Phenylguanidino-4-β-diethylaminoethylamino-5:6-dimethylpyrimidine, 2-*p*-chloro-, and its dihydrochloride, 578.
2-Phenylguanidino-4-β-diethylaminoethylamino-5:6-*cyclo*hexenopyrimidine, 2-*p*-chloro-, 579.
2-Phenylguanidino-4-β-diethylaminoethylamino-6-methyl-5-*iso*amylpyrimidine, 2-*p*-chloro-, 578.
2-Phenylguanidino-4-β-diethylaminoethylamino-6-methyl-5-*n*-butylpyrimidine, 2-*p*-chloro-, 578.
2-Phenylguanidino-4-β-diethylaminoethylamino-6-methyl-5-ethylpyrimidine, 2-*p*-chloro-, 578.
2-Phenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine, 2-*p*-amino-, 581.
4-Phenylguanidino-2-β-diethylaminoethylamino-6-methylpyrimidine, 4-*p*-chloro-, 591.
4-Phenylguanidino-6-β-diethylaminoethylamino-2-methylpyrimidine, 4-*p*-chloro-, 593.
2-Phenylguanidino-4-β-diethylaminoethylamino-5:6-*cyclo*pentenopyrimidine, 2-*p*-chloro-, 578.
2-Phenylguanidino-4-β-diethylaminoethylamino-6-phenylpyrimidine, 2-*p*-chloro-, 578.
2-Phenylguanidino-4-β-diethylaminoethylaminopyrimidine, 2-*p*-chloro-, 578.
2-Phenylguanidino-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine, 2-*p*-chloro-, and its dipicrate, 585.
2-Phenylguanidino-4-γ-diethylaminopropylamino-5:6-dimethylpyrimidine, 2-*p*-chloro-, 578.
2-Phenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-*iso*amylpyrimidine, 2-*p*-chloro-, *di*hydrochloride, 578.
2-Phenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-*n*-butylpyrimidine, 2-*p*-chloro-, 578.
2-Phenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine, 2-*p*-chloro-, 578.
2-Phenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-*n*-propylpyrimidine, 2-*p*-chloro-, and its dihydrochloride, 578.
4-Phenylguanidino-2-γ-diethylaminopropylamino-6-methylpyrimidine, 4-*p*-chloro-, 591.
4-Phenylguanidino-6-γ-diethylaminopropylamino-2-methylpyrimidine, 4-*p*-chloro-, 593.
2-Phenylguanidino-4:6-dimethylpyrimidine, 2-*p*-chloro-, 581.
2-Phenylguanidino-5:6-dimethylpyrimidine, 4-chloro- and 4-hydroxy-2-*p*-chloro-, 577.
2-Phenylguanidino-5:6-*cyclo*hexenopyrimidine, 4-chloro-2-*p*-chloro-, and 4-hydroxy-2-*p*-chloro-, 579.
2-Phenylguanidino-4-hydroxy-6-phenylpyrimidine, 2-*p*-chloro-, 578.
2-Phenylguanidino-6-methyl-5-*n*-propylpyrimidine, 4-chloro-2-*p*-chloro-, 578.
2-Phenylguanidino-4-methylpyrimidine, 4-hydroxy-2-3':5'-*di*chloro-, 579.
2-Phenylguanidino-6-methylpyrimidine, 4-hydroxy-2-(2':5'-*di*chloro-), 579.
4-Phenylguanidino-6-methylpyrimidine, 2-hydroxy-4-*p*-chloro-, hydrochloride, 590.
2-Phenylguanidino-5:6-*cyclo*pentenopyrimidine, 4-hydroxy-2-*p*-chloro-, 579.
***N*-Phenylguanyl-*S*-benzyl*iso*thiourea,** *N*-*p*-chloro-, hydrochloride, 1653.
***N*-Phenylguanyl-*N'*-*n*-butylthiourea,** *N*-*p*-chloro-, and its hydrochloride, 1651.
***N*-Phenylguanyl-*O*-ethyl-*N'*-*iso*propyl*iso*urea,** *N*-*p*-chloro-, and its acetate and hydrochloride, 1652.
***N*-Phenylguanyl-*N'*-ethylthiourea,** *N*-*p*-chloro-, and its hydrochloride, 1651.
***N*-Phenylguanyl-*S*-ethyl*iso*thiourea,** *N*-*p*-chloro-, hydriodide, 1653.
***N*-Phenylguanyl-*S*-methyl-*N'*-*iso*propyl*iso*thiourea,** *N*-*p*-chloro-, and its hydrochloride, 1652.
***N*-Phenylguanyl-*N'*-methylthiourea,** *N*-*p*-chloro-, and its hydrochloride, 1651.
***N*-Phenylguanyl-*S*-methyl*iso*thiourea,** *N*-*p*-chloro-, hydriodide, 1653.
***N*-Phenylguanyl-*N'*-*n*-propylthiourea,** *N*-*p*-chloro-, and its hydrochloride, 1651.
***N*-Phenylguanyl-*N'*-*iso*propylthiourea,** *N*-*p*-chloro-, and its hydrochloride, 1651.
***N*-Phenylguanyl-*S*-*iso*propyl*iso*thiourea,** *N*-*p*-chloro-, hydrobromide, 1653.
Phenylguanylthiourea, *p*-chloro-, and its hydrochloride, 1653.
p-iodo-, hydrochloride, 1654.

4-Phenyl-3:4:5:6:7:8-hexahydrocoumarin, 2015.
4-Phenyl-3:4:5:6:7:8-hexahydrocoumarin-3-carboxylic acid, ethyl ester, 2014.
N^1-Phenyl-N^5-*cyclo*hexyl-N^1-*iso*propyldiguanide, N^1-*p*-chloro-, and its hydrochloride, 1652.
2-Phenyl-4-(1-hydroxyethylidene)oxazol-5-one, 315.
2-Phenyl-4-(1-hydroxypropylidene)oxazol-5-one, 315.
2-Phenylimino-3-acetyl-4-phenylthiazoline, 5-amino-, 5-acetyl derivative, 1266.
2-Phenylindole, 5-chloro-, 870.
2-*p*-**Phenylindole**, and 1-nitroso-, 854.
Phenylmagnesium bromide, use of, for preparation of phenyl aryl sulphides, sulphones, and sulphoxides, 528.
***N*-Phenyl-*N'*-methylacetamidine**, 1521.
***N*-Phenyl-*N'*-methylbenzamidine**, preparation of, 1619.
N^1-Phenyl-N^2-methyl-N^5-*n*-butyldiguanide, N^1-*p*-chloro-, hydrochloride, 1645.
N^1-Phenyl-N^4-methyl-N^5-*n*-butyldiguanide, N^1-*p*-chloro-, and its hydrochloride, 1652.
4-Phenyl-1-(1'-methylbutyl)piperidine-4-carboxylic acid, ethyl ester, and its hydrochloride, 561.
Phenylmethylcarbamyl fluoride, 2186.
2-Phenyl-4-methyl-5-chloromethyliminazole hydrochloride, 734.
N^1-Phenyl-N^2-methyldicyandiamide, N^1-*p*-bromo-, N^1-*p*-chloro-, and N^1-*p*-iodo-, 1639, 1640.
1-Phenyl-2-methyl-2-3'-diethylaminopropylethylene, 1-cyano-, 808.
N^1-Phenyl-N^4-methyl-N^5-diguanide, N^1-*p*-chloro-, and its hydrochloride, 1651.
3-Phenyl-4-methyl-3:4-dihydrophthalazine, 1:4-*di*hydroxy-3-(2'-chloro-5'-nitro-), 209.
1-Phenyl-4-*S*-methyl*iso*dithiobiuret, 1-*p*-chloro-, 1654.
2-Phenyl-5-methylglyoxaline-4-carboxylic acid, and its ethyl ester, 1962.
2-N^1-Phenyl-N^2-methylguanidino-N^3-4-β-diethylaminoethyl-amino-6-methylpyrimidine, 2-N^1-*p*-chloro-, and its trihydrochloride, 593.
2-N^1-Phenyl-N^2-methylguanidino-N^3-4-γ-diethylaminopropyl-amino-6-methylpyrimidine, 2-N^1-*p*-chloro-, and its trihydrochloride, 593.
2-Phenyl-6-methylheptane, 49.
2-Phenyl-6-methylhept-2-ene, 49.
Phenylmethyl*iso*hexylcarbinol, 49.
2-Phenyl-5-methyl-4-hydroxymethyliminazole, and its picrate, 734.
2-Phenyl-5-methyliminazole-4-carboxyaldehyde, and its 2:4-dinitrophenylhydrazone, 734.
2-Phenyl-1-methylindole, 2-*p*-chloro-, and 2-*p*-chloro-3-nitroso-, 854.
2-Phenyl-4-methyloxazole, and its picrate, 1963.
2-Phenyl-5-methyloxazole, and its picrate, 1962.
1-Phenyl-*p*-methylphenacylaniline, 866.
1-Phenyl-*p*-methylphenacyl-*N*-ethylaniline, 867.
1-Phenyl-*p*-methylphenacyl-*N*-methylaniline, 866.
9-Phenyl-10-methylphenanthridinium bromide, 2:9-*p*-*di*amino-, 193.
8:9-*p*-*di*amino-, 195.
chloride, 2:9-*p*-*di*amino-, and its 2-acetyl derivative, and 2-amino-9-*p*-nitro-, 193.
6:9-*p*-*di*amino-, and 6- and 8-amino-9-*p*-nitro-, 195.
3-Phenyl-1-methylphthalaz-4-one, 2':4':6'-*tri*bromo-, 600.
2'-chloro-, 1029.
3'-chloro-, 600.
2'-chloro-5'-amino-, and its acetyl derivative, and 2'-chloro-5'-nitro-, 209.
3-Phenyl-4-methylphthalaz-1-one, and its picrate, 1250.
picrate and sulphate, 600.
3-Phenyl-4-methylphthalaz-1-one, 2':4':6'-*tri*bromo-, and its picrate, 599.
2'-chloro-, and its picrate, 1028.
4'-chloro-, and its picrate, 601.
2'-chloro-5'-nitro-, and its picrate, 208.
3-Phenyl-4-methylphthalaz-1-one-*x*-sulphonic acid, 1251.
***N*-Phenyl-3-methylphthalimidine**, 1251.
***N*-Phenyl-3-methylphthalimidine**, 4'-chloro-, 601.
4-Phenyl-1-methylpiperidine-4-carboxylic acid, ethyl ester. See Pethidine.
N^1-Phenyl-N^2-methyl-N^5-*iso*propyldiguanide, N^1-*p*-chloro-, and its picrate, 1641, 1644.
N^1-Phenyl-N^4-methyl-N^5-*n*- and -*iso*-propyldiguanides, N^1-*p*-chloro-, and their hydrochlorides, 1652.
N^1-Phenyl-N^5-methyl-N^5-*iso*propyldiguanide, chloro-, *p*-cyano-, *p*-iodo-, and *p*-nitro-, hydrohalides, 1635.
5-Phenyl-2-methylpyrimidine-4-carboxylic acid, ethyl ester, 556.
2-Phenyl-4-*p*-methylsulphonylbenzylidene-5-oxazolone, 1506.
4-Phenyl-2-*p*-methylsulphonylphenylthiazole, 1507.
***C*-Phenyl-*N*-methylsydnone**, 2310.
***N*-Phenyl-*S*-methyl*iso*thiourea**, *N*-*p*-chloro-, 590.
***N'*-Phenyl-*S*-methyl*iso*thiourea**, *N*-cyano-*N'*-*p*-bromo-, -*N'*-*p*-chloro-, and -*N'*-*p*-iodo-, 1639.
1-Phenylnaphthalene, 1268.
1-Phenylnaphthalenes, 1270.
1-Phenylnaphthalene, 1-2-amino-, and 1-2-nitro-, 1139.
4:7-*di*amino-, and its dibenzoyl derivative, and 4:7-*di*nitro-, 1268.
1-Phenylnaphthalene-2'-carboxylic acid, 4'-nitro-, 1235.
1-Phenylnaphthalene-2- or **-3-carboxylic acid**, 4':7-*di*nitro-, 1268.
1-Phenylnaphthalene-2':3-dicarboxylic acid, 5:6'-*di*hydroxy-, 1234.
4':7-*di*nitro-, and its derivatives, 1268.
α-Phenyl-β-(2-naphthyl)acrylic acid, 1602.
Phenyl-2-naphthylarsonous acid, 2209.
Phenyl-2-naphthylcyanoarsine, 2211.
1-Phenyl-1-α- and **-β-naphthylethanes**, and their derivatives, 1396.
1-Phenyl-1-α-naphthylethylene, and its trinitrobenzene derivative, 1396.
1-Phenyl-1-β-naphthylethylene, and its derivatives, 1396.
1-Phenyl-2-(α- and -β-naphthyl)ethylenes, 1602.
1-Phenyl-2-β-naphthylethylene, photochemical reaction of, with phenanthraquinone, 2128.
2-Phenyloxazoline, and its methiodide, 1922.
2-Phenyl-Δ^2-oxazoline, addition of hydrogen sulphide to, 1919.
***N'*-Phenyl-*NN*-pentamethylenebenzamidine**, and its salts, 1520.
N^1-Phenyl-N^5:N^5-*cyclo*pentamethylene-N^2-ethyldiguanide, N^1-*p*-chloro-, 1645.
***N*-Phenyl-*N'*-(*NN*-*cyclo*pentamethyleneguanyl)thiourea**, *N*-*p*-chloro-, 1643.
N^1-Phenyl-N^5:N^5-*cyclo*pentamethylene-N^2-methyldiguanide, N^1-*p*-chloro-, 1645.
Phenyl*cyclo*pentanecarboxylic acids, and their derivatives, 974.
3-Phenyl*cyclo*pentanone, derivatives of, 979.
2-Phenyl*cyclo*pentanone-3:5-dicarboxylic acid, dimethyl ester, enol form, 978.
3-Phenyl*cyclo*pentyldimethylcarbinol, 978.
***p*-Phenylphenacyl-*N*-ethylaniline**, 855.
***p*-Phenylphenacyl-*N*-methylaniline**, 855.
9-Phenylphenanthridine, amino- and hydroxy-9-*p*-nitro-derivatives, 195.
2-amino-9-*p*-nitro-, 193.
3-Phenylphthalaz-1-one, and its derivatives, 1250.
3-Phenylphthalaz-1-one, 2':4':6'-*tri*bromo-, and its picrate, 598.
2'-chloro-, and its picrate, 1028.
3'-chloro-, and its picrate, 600.
4'-chloro-, 601.
2'-chloro-5'-amino-, and its acetyl derivative, and 2'-chloro-5'-nitro-, and its picrate, 208.
3-Phenylphthalaz-4-one, 2':4':6'-*tri*bromo-, 599.
2'-chloro-, 1028.
3'-chloro-, 600.
2'-chloro-5'-amino-, and its acetyl derivative, and 2'-chloro-5'-nitro-, 209.
3-Phenylphthalaz-1-one-*x*-sulphonic acid, 1251.
***N*-Phenylphthalimidine**, 2':4'-*di*bromo-, 599.
2'-chloro-, 1028.
3'-chloro-, 600.
4'-chloro-, 601.
N-2:4- and -2:6-*di*nitro-, 1995.
4-Phenylpiperidine-4-carboxylic acid, ethyl ester. See Norpethidine.
Phenylpropenylcarbinol, kinetics of acid-catalysed rearrangement of, in solvent mixtures, 1982.
Phenylpropiolic acid, esters, 679.
Phenylpropiolic acid, *p*-nitro-, dimerisation of, 1267.
Phenylpropiolic acids, 1267.
β-Phenylpropionic acid, $\alpha\beta$-*di*cyano-, ethyl ester, 977.
α-oximino-β-bromo- and -β-chloro-, 1254.
Phenyl *p*-*n*-propoxy benzyl ketone, 152.

N^1-Phenyl-N^4-*n*-propyl-N^5-*n*-butyldiguanide, N^1-*p*-chloro-, and its hydrochloride, 1652.
N^1-Phenyl-N^5-*iso*propyl-N^3-*n*-butyldiguanide, N^1-*p*-chloro-, hydrochloride, 1644.
N^1-Phenyl-N^5-*iso*propyldiguanide, bromo-, chloro-, cyano-, fluoro-, iodo-, and nitro-derivatives, 1634, 1635.
N^1-*p*-bromo-, and N^1-*p*-chloro-, 1643.
***N*-Phenyl-*N'*-*iso*propylguanyl-*S*-ethyl*iso*thiourea**, *N*-*p*-chloro-, hydrobromide, 1642.
***N*-Phenyl-*N'*-*iso*propylguanylthiourea**, *N*-*p*-bromo-, and *N*-*p*-nitro-, 1643.
N-*p*-chloro-, 1642.
4-Phenyl-1-*iso*propylpiperidine-4-carboxylic acid, ethyl ester, 561.
N^1-Phenyl-N^4-*n*-propyl-N^5-*iso*propyldiguanide, N^1-*p*-chloro-, and its hydrochloride, 1652.
***N*-Phenyl-N^1-2-pyridylbenzamidine**, and its derivatives, 1520.
2-Phenylpyrrolidine, and its picrate, 187.
2-Phenyl-Δ^3-pyrroline, and 2-*p*-chloro-, and 2-*m*-hydroxy-, and their picrates, 187.
Phenylpyruvic acid, *p*-hydroxy-, methyl ester, 2:4-*di*nitrophenylhydrazone, 260.
2-nitro-5-hydroxy, and its derivatives, 1607, 1608.
2-Phenylquinoline, 4'-amino-, 4-*p*-nitrocinnamylidene derivative, 2010.
Phenylquinolines, and their picrates, 2220.
2-Phenylquinoline-4-carboxylic acid, 2-*p*-amino-, acetyl and benzylidene derivatives, and 2-*p*-oximinoamino-, acetyl derivative, 2010.
α-Phenyl-β-(6-quinolyl)acrylic acid, 2152.
2-Phenyl-1-(6-quinolyl)ethanol, 2152.
Phenylsulphonyl-. See also Benzenesulphonyl-.
***p*-Phenylsulphonylacetophenone**, 603.
***p*-Phenylsulphonylbenzaldehyde**, and 4-*p*-chloro-, 602.
***p*-Phenylsulphonylbenzophenone**, 603.
***p*-Phenylsulphonylbenzylammonium** chloride, 382.
4-Phenylsulphonylbenzylidene *di*acetate, 4-*p*-chloro-, 602.
***N*-Phenylsydnone**, *N*-*m*- and -*p*-bromo-, and *C*-chloro-, 2310.
3-Phenyl-5:6:7:8-tetrahydrophenanthridine, and its picrate, 1540.
1-Phenyl-3:1':3':3'-tetramethyl-2'-ethylideneindolylidene-5-pyrazolone, 690.
4-Phenylthiazole, 5:2-*di*amino-, 2-benzoyl derivative, 1266.
Phenyl-2-thienylchloroarsine, 2211.
Phenyl-2-thienylcyanoarsine, 2211.
Phenyl 2-thienyl sulphone, 526.
Phenyl 2-thienyl sulphone, *p*-amino-, and *p*-nitro-, 527.
2:5-*di*hydroxy-, 527.
3-Phenylthioacetamido-2-(2'-carboxy-3'-thionaphthenylcarbamyl)thionaphthen, 3-*o*-cyano-, 81.
3-Phenylthioacetamido-2-6'-ketothionaphtheno(2'':3'':5:4)-1:3-oxazinyl-2'-thionaphthen, 3-*o*-cyano-, 81.
Phenylthioacetic acid, derivatives, conversion of, into thionaphthens, 81.
Phenylthiol, 2:4-*di*amino-, *di*hydrochloride, 1004.
β-Phenylthiopyruvic acids, bromo- and chloro-, 1254.
4-Phenylthioquinazoline, *di*chloro-derivatives, and 4-hydroxy-2-*p*-chloro-, 1772.
β-5-Phenyl-2-thiothiazolidone-4-carboxyamide, 1339.
5-Phenyl-2-thiothiazolidone-4-carboxylic acid, 1338.
5-Phenylthioureido-2-anilino-4-carbethoxythiazole, 2031.
2-Phenylthioureido-4-dialkylaminoalkylamino-6-methylpyrimidines, 581.
2-Phenylthioureido-4-β-diethylaminoethylamino-6-methyl-5-ethylpyrimidine, 2-*p*-chloro-, 584.
2-Phenylthioureido-4-β-diethylaminoethylamino-6-methylpyrimidine, 2-*p*-bromo-, and 2-*p*-chloro-, 584.
4-Phenylthioureido-2-β-diethylaminoethylamino-6-methylpyrimidine, 4-*p*-chloro-, 592.
4-Phenylthioureido-6-β-diethylaminoethylamino-2-methylpyrimidine, 4-*p*-chloro-, 592.
2-Phenylthioureido-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine, 2-*p*-chloro-, and its dihydrochloride, 585.
2-Phenylthioureido-4-γ-diethylaminopropylamino-6-methylpyrimidine, 2-*p*-chloro-, 585.
4-Phenylthioureido-6-γ-diethylaminopropylamino-2-methylpyrimidine, 4-*p*-chloro-, 593.
Phenyltolylarsonous acids, 2209.
Phenyltolylarsonous acids, chloro-, and nitro-, 2209.
Phenyltolylchloroarsines, nitro-, 2210.
Phenyltolylcyanoarsines, and chloro-, and nitro-, 2211.
2-Phenyl-3-*p*-tolyl-1-ethylindole, 866.
3-Phenyl-2-*p*-tolyl-1-ethylindole, 866.
2-Phenyl-3-*p*-tolylindole, and its picrate, 866.
3-Phenyl-2-*p*-tolylindole, and its picrate, 866.
2-Phenyl-3-*p*-tolyl-1-methylindole, 866.
3-Phenyl-2-*p*-tolyl-1-methylindole, 866.
Phenyl *p*-tolyl sulphone, *p*-chloro-, 602.
N^1-Phenyl-N^3:N^5:N^5-trimethyldiguanide, N^1-*p*-chloro-, acetate, 1645.
3-Phenylundecan-2-one, and its derivatives, 1744.
α-Phenylureidobenzyl cyanide, 1266.
2-Phenylureido-4-dialkylaminoalkylamino-6-methylpyrimidines, 581.
2-Phenylureido-4-di-*n*-butylamino-6-methylpyrimidine, 2-*p*-chloro-, 584.
2-Phenylureido-4-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine, 2-*p*-chloro-, 584.
2-Phenylureido-4-δ-diethylaminobutylamino-6-methylpyrimidine, 2-*p*-chloro-, 584.
2-Phenylureido-4-β-diethylaminoethylamino-6-methyl-5-ethylpyrimidine, 2-*p*-chloro-, 584.
2-Phenylureido-4-β-diethylaminoethylamino-6-methylpyrimidine, 2-*p*-chloro-, 584.
2-Phenylureido-4-γ-diethylaminopropylamino-6-methylpyrimidine, 2-*p*-chloro-, 584.
2-Phenylureido-6-methylpyrimidine, 4:2-*p*-*di*chloro-, 583.
4-hydroxy-2-*p*-chloro-, 583.
2-Phenylureido-4-morpholino-6-methylpyrimidine, 2-*p*-chloro-, 584.
2-Phenylureido-4-piperidino-6-methylpyrimidine, 2-*p*-chloro-, 584.
δ-Phenylvaleric acid, preparation of, 169.
Phenylvinylmethyl radical, 1111.
Phenyl-*m*-4-xylylarsonous acid, 2209.
2-*p*-Phenylyl-1-ethylindole, and 3-nitroso-, 854.
3-*p*-Phenylyl-1-ethylindole, 855.
2-*p*-Phenylyl-1-methylindole, and 3-nitroso-, 854.
2-*p*-Phenylyl-5-methylindole, and 1-nitroso-, 854, 855.
3-*p*-Phenylyl-1-methylindole, 855.
Phosphorus *tri*bromide, preparation of, 1846.
oxy*di*chlorofluoride, preparation of, 1011.
Phosphorus organic compounds, esters, 695, 699, 1010, 1313.
Phosphorylation, 1106.
Photochemical oxidation with dichromate, kinetics of, 2119.
reactions, 2126.
Phthalazine derivatives, 777.
from aniline, 1249.
ω-Phthalimido-*o*-aminoacetophenone, and *x*-nitro-, *o*-acetyl derivatives, 1174.
***p*-Phthalimidobenzenesulphonamide**, preparation of, 822.
***p*-Phthalimidobenzenesulphonamidomethane**, 823.
2-(*p*-Phthalimidobenzenesulphonamido)pyridine, 823.
2-(*p*-Phthalimidobenzenesulphonamido)thiazole, 823.
ω-Phthalimido-*o*-hydroxyacetophenone, 1174.
N^4-Phthalyl-N^1-methylsulphanilamide, 823.
N^4-Phthalyl-N^1-phenylsulphanilamide, 823.
N^4-Phthalylsulphanilamide, derivatives, synthesis of, 821.
preparation of, 822.
N^4-Phthalylsulphapyridine, 823.
N^4-Phthalylsulphathiazole, 823.
Physical properties and constitution, 607, 610, 616, 624, 644, 654, 658, 674, 1804, 1809, 1814, 1820, 1825, 1833.
2-Picoline, 3-amino-, diacetyl derivative, and its picrate, 200.
3-Picoline, 4-amino-, and 4-hydroxy-, and their derivatives, 199.
Piperidine, derivatives, synthesis of, 2011.
Piperidine series, 806.
ω Piperidinoacetanilide, *p*-chloro-*o*-amino- and -*o*-nitro-, 1910.
2-Piperidino-6-amino-4-styrylpyrimidine, 5-nitro-, 1132.
Piperidinoanthanthrone, 1181.
2-Piperidino-4:6-bis-(4-dimethylaminostyryl)pyrimidine, 2150.
β-Piperidinobutyranilide, *p*-chloro-*o*-amino- and -*o*-nitro-, 1911.
2-Piperidino-4-[2-(4-dimethylaminophenyl)ethyl]-6-methylpyrimidine, 2151.
2-Piperidino-4-(4-dimethylaminostyryl)-6-methylpyrimidine, 2150.
6-Piperidino-4-(*p*-dimethylaminostyryl)pyrimidine, 1715.
2-Piperidino-4:6-dimethylpyrimidine, 2151.

2-Piperidino-4:6-distyrylpyrimidine, 2151.
2-Piperidinoethylbenzyl cyanide, and its picrate, 809.
2-Piperidinomethylbenziminazole, 5(or 6)-chloro-, and its hydrochloride, 1911.
2-Piperidino-5-methylhexyl cyanide, 5-nitro-, 231.
γ-Piperidino-α-phenylbutyric acid, ethyl ester, 809.
2-γ-Piperidinopropylamino-4-hydroxyquinazoline, hemihydrate, 1770.
2-γ-Piperidinopropylaminoquinazoline, 4-chloro-, 1770.
2-Piperidino-4-styryl-6-methylpyrimidine, 2151.
Piscidia erythrina, constituents of root bark of, 257.
Piscidic acid, structure of, and its derivatives, 257.
Plane trees. See *Platanus acerifolia*.
Plasma albumin. See under Albumin.
Platanol, dehydrogenation of, 951.
Platanus acerifolia, bark, betulinic acid from, 948.
Platinum bases :—
Bromotriamminoplatinous salts, 1914.
Carbonatotriamininoplatinum, 1914.
Chlorotriaminoplatinous salts, 1913.
Ethylenediaminodiamminoplatinous picrate, 1915.
Ethylenediaminotriamminoplatinous chloride, 1915.
Nitratotriamminoplatinous nitrate, 1914.
Nitrotriamminoplatinous salts, 1914.
Oxalatotriamminoplatinum, 1915.
Picratotriamminoplatinous picrate, 1914.
Platinous triammines, 1912.
Sulphatotriamminoplatinum, and its hemihydrate, 1914.
Pleiadene-7:12-dione, 1-amino-, 1758.
Pneumococcus, types I, II, and III, physical properties of specific polysaccharides from, 1561.
Podocarprene, identity of, with kaurene, 1888.
Podocarpus, podocarprene from, 1888.
Poisons, catalyst, detoxication of, 1091, 1093, 1916.
Polarity of bonds, 401.
Polymethylbenzenes, 2154.
Polyquinolyls, 2008.
Polysaccharides, specific, from *Mycobacterium tuberculosis*, 1211, 1220.
specific, from types of *Pneumococcus*, 1561.
Polysiphonia fastigiata, evolution by, of dimethyl sulphide and its precursor, 1591.
Polystyrene, solution and diffusion of gases in, at high pressures, 1541.
Polysulphides. See *poly*Sulphides.
Potassium bromo*tetra*fluoride, 2136.
Potassium organic compounds :—
Potassium *tert.*-butoxide, fission of non-enolisable ketones by, 1408.
Potato starch. See under Starch.
*allo*Pregnan-20-on-3(β)-yl benzoate, 791.
Pregn-5-en-20-on-3(β)-yl benzoate, 791.
Primulaverin, 2220.
Prins reaction, 89.
Proflavine, absorption of, by cells of *Bacterium lactis aerogenes*, 2290.
bacteriostatic action of, effect of pH on, 1235.
Progesterone, synthetic analogues of, 1078.
Propane, 1:2-*di*chloro-2-nitro-, and 1:2:3-*tri*chloro-2-nitro-, 2321.
*cyclo*Propanecarboxylic acid, and its esters, preparation of, 1805.
*cyclo*Propane-1:1-dicarboxylic acid, preparation of, and its esters, 1806.
Propanethiol, 2-hydroxy-, 39.
Propanol, 2:3-*di*mercapto-, preparation of, from 2:3-dichloropropanol, 1393.
1-Propenylbenzene, spectrum of, absorption, 1124.
2-Propenylbenziminazole, 5(or 6)-chloro-, 1911.
Propenylethynylcarbinol, and its acetate, rearrangement and hydrolysis of, 794.
Propionic acid, α-fluoro-, methyl ester, 1777.
2-Propionylcarbamylthionaphthen, 2-hydroxy-, and its *O*-acetyl derivative, 83.
Propionylcarbinyl benzoate, and its semicarbazone, 275.
β-Propionylcrotonolactone, α-hydroxy-β-β′-chloro-, α-acetyl derivative, 1298.
4-Propionyl-3-methylphenol, 6-amino-, and 6-nitro-, 2146.
N-Propionyl-*p*-toluenesulphonamide, 112.
Propiophenone, nitration of, 356.
Propiophenone, *o*- and *m*-amino-, *m*-bromo-, 5-bromo-2-amino-, 5-bromo-2-nitro-, 5-chloro-2-amino-, 5-chloro-2-nitro-, 3- and 5-nitro-2-amino-, and their derivatives, 356, 357.
p-amino-, and its acetyl derivative, azines of, 685.
2′-*n*-Propoxydiethyl sulphilimine, 2179.
2-*n*-Propoxydiethyl sulphone, 2-chloro-, 2179.
***p*-*n*-Propoxyphenylacetic acid**, ethyl ester, 153.
***n*-Propyl** nitrate, preparation and physical properties of, 1847.
2-*iso*Propylamino-6-hydroxy-4-methyltriazine, 1369.
N^1-*iso*Propyl-N^3-*n*-butyldicyandiamide, 1650.
***n*-Propylcarbamic acid**, 2- and 3-chloro-, 2:3-*di*chloro-, *N*-nitroso-2- and -3-chloro-, and *N*-nitroso-2:3-*di*chloro-, methyl esters, 2320.
2-*n*-Propylcinchoninic acid, and 6-bromo-, and 6-bromo-4-hydroxy-, 108.
***iso*Propyldicyandiamide**, 1369.
Propyldicyandiamides, 1633.
***n*-Propyldimethylsulphonium** salts, olefin formation from, 2072.
***iso*Propyldimethylsulphonium** salts, olefin formation from, 2077.
Propylene, 3:3:3-*tri*chloro-1-nitro-, 1989.
***iso*Propylguanidine**, sulphate, 1641.
N^3-*iso*Propylguanidinobenziminazole, and 5-chloro-, and their salts, 1369.
2-(N^3-*iso*Propylguanidino)benziminazole, 5:6-*di*chloro-, and its salts, 1370.
2-(N^3-*iso*Propylguanidino)-5:6-dimethoxybenziminazole, and its salts, 1370.
2-(N^3-*iso*Propylguanidino)-5:6-dimethylbenziminazole, and its salts, 1370.
2-(N^3-*iso*Propylguanidino)-5-methoxybenziminazole, and its salts, 1370.
2-(N^3-*iso*Propylguanidino)-5-methylbenziminazole, and its salts, 1370.
***N*-*iso*Propylguanyl-*S*-methyl*iso*thiourea**, hydriodide, 1654.
***iso*Propylguanylthiourea**, 1654.
***trans*-2-Propyl*cyclo*hexylbenzamide**, 2-3′-bromo-, 1375.
N^1-*iso*Propyl-N^3-*cyclo*hexyldicyandiamide, 1650.
5-Propylhydantoin-5-acetic acid, ethyl ester, 1389.
***iso*Propylidenemalonic acid**, calcium salt, 1684.
4-*iso*Propylidene-2-thiothiazolone, 1339.
***n*-Propylmalonic acid**, esters, 633.
***iso*Propyl nonyl ketone**, 1745.
1-*iso*Propyl*cyclo*pentane-3:4-bis-(β-butyric acid), 168.
1-*iso*Propyl*cyclo*pentane-3:4-bis-(α-propionic acid), and its di-*p*-phenylphenacyl ester, 167.
***p*-*iso*Propylphenol**, preparation of, 166.
N^1-*n*-Propyl-N^3-*iso*propyldicyandiamide, 1650.
γ-*iso*Propylsuberic acid, 168.
α-Propylsuccinic acid, α-amino-, 1389.
***p*-Propylsulphonylbenzylammonium** chlorides, 382.
***p*-*iso*Propylsulphonylphenyl** cyanide, 383.
***N*-*iso*Propylthiobenzamide**, 1924.
2′-*n*-Propylthiodiethyl sulphide, 2-chloro-, 2179.
2-*n*-Propylthiopyridine, 5-amino-, and its hydrochloride, and 5-nitro-, 1944.
***N′S*-Propyl*iso*thioureas**, *N*-cyano-, 1633.
Proteins, adsorption on, of water vapour, 1083.
Protocatechuic aldehyde. See Benzaldehyde, 4:5-*di*hydroxy-.
Prototropy, three-carbon, 17.
Provitamin-D_3. See 7-Dehydrocholesterol.
Pseudomonas mors-prunorum, levan produced from sucrose by, 1560.
Purine nucleosides, synthesis of, 957, 965, 967, 1685.
Purpurogallin, 1045.
structure of, 116.
Pyrazine derivatives, 1855, 1859, 1862.
Pyrazine, amino-, derivatives, synthesis of, 1855.
hydroxy-, derivatives, preparation of, 1862.
Pyrazines, 2-chloro-, oxidation of, with hydrogen peroxide, 1859.
Pyridazine derivatives, from sucrose, 2191, 2195, 2199.
3-Pyridazine-6-carboxylic acid, 3-chloro-, 2198.
3-Pyridazone-6-carboxylic acid, ethyl ester, hydrate, 2197.
methyl ester, 2194.
Pyridine, catalytic hydrogenation of, self-poisoning in, 1093.
derivatives, 2:5-disubstituted, 1939.
reactions of, with acyl peroxides, 2218.
Pyridine, 2:3-*di*amino-, 5-bromo-2:3-*di*amino-, and its derivatives, and 5-bromo-3-nitro-2-amino-, 1391.

Pyridine, 2:3:6-*tri*amino-, triacetyl derivative, 1392.
2-chloro-5-cyano-, and 5-cyano-2-mercapto-, 1942.
2-hydroxy-, 1-oxide, and its copper salt, 1866.
Pyridinium benzenesulphonate, 2-amino-, 1522.
salts, reaction of, with tetra-arylglycols, 385.
Pyridoacridine, derivatives, 123.
1:2:2′:3′-Pyridoacridine, 5-amino-, 5-chloro-, 5-chloro-4-fluoro-, and 4-fluoro-5-amino-, and their derivatives, 290.
1:2:3′:2′-Pyridoacridine, 5:8-*di*chloro-, 126.
3:4:3′:2′-Pyridoacridine, 5:8-*di*chloro-, 126.
4-*N*-Pyridylacetamido-2-methyl-1-naphthol chloride, 185.
β-Pyridyl(4)alanine *di*hydrochloride, 88.
***N*-Pyridyl(4)-*p*-aminobenzoic acid**, and its hydrochloride, 241.
2-(2′-Pyridylamino)-4-β-diethylaminoethylamino-6-methylpyrimidine, and its dihydrochloride, 595.
4-(2′-Pyridylamino)-2-β-diethylaminoethylamino-6-methylpyrimidine, 596.
3-(2′-Pyridylamino)-4-hydroxy-6-methylpyrimidine, 595.
2-(2′-Pyridylamino)-6-methylpyrimidine, 4-chloro-, 595.
Pyridylaminopyrimidines, 594.
***o*-Pyridylbenzoic acid**, methyl ester, picrates, 2219.
***N*-2-Pyridyl-*N′*-methylacetamidine**, 1521.
β-Pyridyl(4)propionic acid, α-oximino-, and its ethyl ester, 88.
***S*-2-Pyridylthiuronium** chloride, *S*-5-cyano-, 1942.
Pyrimidine, 2:4:5-*tri*amino-6-hydroxy-, 5-acetyl, 5-*p*-acetylbenzenesulphonyl, and 5-*p*-aminobenzenesulphonyl derivatives, 1159, 1161.
5-benzoyl and 5-α-hydroxypropionyl derivatives, 1160.
Pyrimidines, substituted, spectra of, infra-red, 2265.
Pyrimidylaminopyrimidines, 594.
Pyrimidyl-5-oxamic acid, 2:4-*di*amino-6-hydroxy-, and its sodium salt, 1160.

Q.

Quinaldine, 6-bromo-4-hydroxy-, and its picrate, 108.
Quinazoline, 2:4:6- and 2:4:7-*tri*chloro-, 6- and 7-chloro-2:4-*di*hydroxy-, 2:4-*di*chloro-6- and 7-nitro-, and 7-nitro-2:4-*di*hydroxy-, 1762, 1763.
6- and 7-nitro-4-amino-, and their acetyl derivatives, 364.
6- and 7-nitro-4-hydroxy-, reactions of, and their derivatives, 360.
Quindoline, quaternary salts, ψ-bases from, 919.
Quinindoline, preparation of, 923.
Quinindoline, 9-amino-, and 9-nitro-, and their acetyl derivatives, 924.
Quinol, clathrate compound of, with methyl alcohol, 571.
compounds of, and their structure, 65, 815.
condensation of, with benzoin, 1992.
Quinols, preparation of alkyl ethers of, 2303.
α-Quinol, structure of, 69.
Quinoline, derivatives, synthesis of, by Pfitzinger reactions, 106.
Quinoline, 4-amino-, nitration of, 2023.
4-chloro-3-nitro- and 3-nitro-4-amino-, 1288, 1289.
6-fluoro-8-amino- and -8-nitro-, 289, 290.
2-hydroxy-, 1-oxide, preparation of, 1866.
4-hydroxy-, derivatives, from arylamines and ethyl ethoxymethylenemalonate, 893.
3-nitro-, *Bz*-substituted, 2024.
6-nitro-2- and -4-amino-, 8-nitro-4-amino-, and their derivatives, 1708, 1709.
6-nitro-4-amino-, 3(?):6-*di*nitro-4-amino-, 3(?):6-*di*nitro-4-hydroxy-, and 6-nitro-4-nitroamino-, 2024.
***iso*Quinoline**, derivatives, 777.
Quinolines, 4-chloro-, and 6-nitro-, 1707.
4-hydroxy-, synthesis of, 106.
4-substituted, 93.
***N*-Quinoline-*p*-aminobenzoic acids**, 241.
Quinoline-3:4-dicarboxylic acid, 2-hydroxy-, 554.
4-Quinolinol, 6-amino-, 1289.
β-6-Quinolylacraldehyde, 2010.
2′-[4″-(6‴-Quinolyl-β-acrylidene)aminophenyl]-2:6′-diquinolyl, 2011.
β-Quinolyl(4)alanine, and its derivatives, 88.
5′-Quinolylanthranilic acid, 4-chloro-, 126.
7′-Quinolylanthranilic acid, 7-chloro-, and its ethyl ester, 126.
***N*-(8′-Quinolyl)anthranilic acid**, and *N*-6′-fluoro-, 290.
1-α-Quinolylbenztriazole, 923.
5-(2′-Quinolylmethylene)hydantoin, 1389.
5-(2′-Quinolylmethyl)hydantoin, 1389.
β-2-Quinolylpropionic acid, α-amino-, 1389.
β-Quinolyl(4)propionic acid, α-oximino-, and its ethyl ester, 88.
***N*^{1}-6-Quinolyl-*N*^{5}-*iso*propyldiguanide**, and *N*^{1}-8-chloro-, hydrochloride, 1635.
Quinones, αβ-unsaturated, halogen addition to, 980.
Quinoxaline, derivatives, 777.
Quinoxaline, 5- and 6-amino-, preparation of, 2132.
2:3:6-*tri*chloro-, 3-chloro-2-amino-, and 2:6-*di*chloro-3-amino-, 781.
2-hydroxy-, oxidation of, and of its derivatives with hydrogen peroxide, 519.
2:3-*di*hydroxy-, preparation of, 521.
Quinoxaline-3-carboxyamide, 2-amino-, conversion of, into alloxazine, 517.
Quinoxaline-3-carboxylic acid, 2-amino-, 2-acetyl derivative, amide and methyl ester, 518.

R.

Radioactive elements, fluorides of, 1991.
Reactions between non-bonded atoms, 340.
elimination, mechanism of, 2038, 2043, 2049, 2055, 2058, 2065, 2072, 2077, 2084, 2090, 2093.
Reactivity, cationoid, of aromatic compounds, 1175.
Reduction of polynitro-compounds, 1275.
Refractivity of acetals, 616.
of acetylenic compounds, 674.
of aliphatic acids and alcohols, 1814.
of aliphatic carboxylic esters, 624.
of aliphatic disulphides, sulphides, and thiols, 1820.
of *n*-alkylbenzenes, 607.
of amines, 1825.
of compounds with 3- and 4-membered carbon rings, 1804.
of compounds with 5- and 6-membered carbon rings, 1809.
of cyanides, 674.
of esters of oxy-acids and of nitro-paraffins, 1833.
of ethers, 616.
of ethylenic compounds, 658.
of halogens, 644.
of ketones, 610.
of α-naphthyl and phenyl groups, 654.
Repandine, 2170.
Report of the Council, 541.
Resin acids, diterpenoid, stereochemistry of, 1197.
Resorcinol, condensation of, with benzoin, 1992.
Respropiophenone, ω-chloro-, and ω-hydroxy, 1611.
Rhodanine, preparation of, 1253.
9-β-D-Ribofuranosidoadenine, 2:8-*di*chloro-, 968.
9-β-D-Ribofuranosidoguanine, 1687.
9-D-Ribopyranosidoxanthine, synthesis of, 523.
Ribose, chemistry of, and its derivatives, 2035.
1-D-Ribosidoglyoxaline-4:5-dicarboxyamide, 524.
9-D-Ribosidoxanthine, 524.
Rice starch. See under Starch.
Rotation, molecular, and structure of steroids, 783, 1354, 1357.
Rotenone, analogues of, 1672.
synthesis of, and its derivatives, 1610.
Rottlerin, 113.
Rottlerone change, 115.
Rubiadin dimethyl ether, 567.
Rubiadin-1 methyl ether, and its derivatives, 567.

S.

Salicylic acid, 5-hydroxy-, preparation of, 2221.
Schiff's bases from nitromalondialdehyde, 2026.
Schmidt rearrangement, 1713.
Scopoletin β-gentiobioside, and its hepta-acetyl derivative, 1672.
Scopoletin-3-carboxylic acid, 1672.
Selenium, photochemistry of, 766.
Semicarbazones, reaction of, with nitrous acid, ketones formed by, 2319.
Senecio alkaloids, 1891.

Senecio kirkii, alkaloid from, 1891.
Senkirkine, and its salts, 1892.
Silica. See Silicon *di*oxide.
Silica gel, preparation of, 2251.
Silicon *di*oxide, vitreous, deposition of carbon on, 1362.
Silver bromo*tetra*fluoride, 2137.
Soaps, zinc, solubility of, in organic solvents, 1750.
Sodium hydrogen sulphide, solution, rapid preparation of, 242.
Sodium organic compounds :—
Sodium aryldiazoates, decomposition reactions of, 556.
benzenediazoate, reactions of, 349.
decyl sulphate, soluble films of, expansion of, at air–water and toluene–water interfaces, 943.
Solubility of gases, measurement of, 2033.
Solutions, thermochemistry of, 1016, 1019.
Solvents, aqueous and non-aqueous, nature of hydrogen ions in, 1976.
effect of, on rates and product-proportions of elimination reactions, 2043.
non-aqueous, acid–base catalysis in, 370.
oxygen-containing, proton affinities of, 1971.
Sophora alkaloids, 1889.
Sorbates, 133.
Sorbitol, ethylidene derivatives of, 1933.
Spectra, absorption, infra-red, of anthraquinone derivatives, 1441.
of fluorinated hydrocarbons, 1428, 1432.
of mixtures of alcohols and aldehydes, 1454.
of terpenoids, 1412.
vibrational frequency of carbonyl group in, 1436.
of terpenoid compounds, 1306.
ultra-violet, of 2-amino- and 2-imino-3-methyl-2:3-dihydrobenzthiazoles, 1497.
vibrational, correlation of, with molecular structure, 328.
γ-Spinastenol, and its esters, 1356.
Spinels, properties of, at high temperatures, 1729.
Starch, acorn, structure of, 1779.
amylolysis of, 924.
fractionating agents for, 1687.
maize, 31.
potato, 30.
rice, 31.
structure of, 27.
sweet potato, 31.
Steroids, structure of, from molecular rotation, 783, 1354, 1357.
Walden inversion and, 1032, 1043.
Steroid series, syntheses in, 162.
*neo***Sterol**, constitution of, 1357.
Sterol group, 1783, 1788, 1792, 1798.
Stigmasta-5:22-dien-3-(β)-yl benzoate, 22:23-*di*bromide, 793.
Stilbene, analogues, heterocyclic, 2147.
photochemical reactions of, with 1:2:3-triketones, 2128.
Stilbene, α:4′-*di*cyano-, and α:4:4′-*tri*cyano-, 1025.
2:4:6:2′:4′-*penta*nitro-, 1614.
2:6-*di*nitro-4-amino-, and its acetyl derivative, 1277.
Stilbenes, *poly*nitro-, nitration of, 1612.
Stilbenecarboxylic acids, 1024.
Stilbene-4-carboxylic acid, and its anilide, 226.
Stilbene-4-carboxylic acid, α-cyano-, 1025.
Stilbenedicarboxylic acids, and their derivatives, 1025.
Stilbene-4:4′-dicarboxylic acid, α-cyano-, 1025.
Stilbene-α:4:4′-tricarboxylic acid, 1025.
Strecker degradation, 176.
Strychnine, 703, 951.
reduction of, and of its derivatives, 1661.
*neo***Strychnine**, experiments with, 951.
*neo***Strychnine**, *x*-hydroxy-, 955.
ψ-Strychnine, experiments with, 951.
preparation of, 703.
sec.-**ψ-Strychnine**, derivatives of, 954.
Styrene, polymerisation of, propagation of reaction chains in, 2232.
short-chain, in presence of hydrogen chloride and stannic chloride, 1867.
reaction of, with naphthalene, 1397.
Styrene, 2-β-*di*nitro-5-hydroxy-, 5-acetyl derivative, 1609.
2:β-*di*nitro-6-hydroxy-, 6-acetyl derivative, 1608.
β:2-*di*nitro-4:5-*di*hydroxy-, 4:5-diacetyl derivative, 2224.
2-Styrylbenzoxazole, and its picrate, 2153.
4-Styrylbenzyl alcohol, 225.
2-Styryl-6:7-benzquinoline, 4-amino-, 4-acetyl derivative, 1293.
2-Styryl-7:8-benzquinoline, 6-nitro-, 1295.
4-Styrylbenzylamine, 224.
and its benzoyl derivative, 226.
4-Styrylbenzylcarbamic acid, ethyl ester, 226.
4-Styrylbenzyldimethylamine, 224.
and its picrate, 227.
4-Styrylbenzylmethyl ether, 225.
4-Styryl-4-deoxyleucopterin, 1133.
2-Styrylfuran, 2-4-amino-, and its acetyl derivative and 2-4-nitro-, 2154.
4-Styryl-6-methylpyrimidine, 2-chloro-, 2151.
6-Styryl-1-methyl-1:2:3:4-tetrahydroquinoline, 2153.
4-Styrylphenylacetamide, 226.
4-Styrylphenylacetic acid, and its anilide, 226.
4-Styrylphenylacet-thiomorpholide, 225.
4-Styrylphenylmethylcarbamic acid, methyl ester, 226.
6-Styrylpteridine, 2:8:9-*tri*hydroxy-, 1132.
4-Styrylpurine, 2-amino-8-hydroxy- and 2-chloro-8-hydroxy-, 1132, 1133.
4-Styrylpyrimidine, derivatives, 1128.
4-Styrylpyrimidine, 2:5:6-*tri*amino-, 2-chloro-5:6-*di*amino-, 2-chloro-5-nitro-6-amino-, 2:6-*di*chloro-5-nitro-, and 5-nitro-2:6-*di*amino-, 1132, 1133.
2:5-6-*tri*amino-4-*p*-amino-, 2:6-*di*chloro-5-nitro-4-*p*-nitro- and 5-nitro-2:6-*di*amino-4-*p*-nitro-, 1134.
2-Styrylquinoline, 6-amino- and 6-nitro-2-4-nitro-, 2152.
6-Styrylquinoline, 2152.
6- and 8-Styrylquinolines, 6- and 8-4-amino-, and -4-nitro-, 2151, 2152.
4-Styryluracil, 5-nitro-, and its derivatives, 1131.
5-nitro-4-*p*-nitro-, 1134.
Substitution at a saturated carbon atom, 1283.
in aromatic compounds, transition state in, 727.
Succinic acid, heat of ionisation of, 1019.
Sucrose, conversion of, into furan compounds, 155.
into pyridazine derivatives, 2191, 2195, 2199.
dextran synthesised from, by *Betacoccus arabinosaceus*, 1555.
levan produced from, by *Pseudomonas mors-prunorum*, 1560.
Sugars, aldose, oxidation of, by iodine solutions, 810.
mixed, analysis of, by partition chromatography, 1679.
***p*-Sulphamylbenzaldehyde**, 603.
***N*¹-Sulphanilamides** from aminoquinoxalines, 2129.
5-Sulphanilamido-2:6-dimethyl-3-pyridazone, and its hydrochloride, 2197.
2-Sulphanilamidoethylthiol hydrochloride, 1925.
Sulphides, aliphatic, physical properties and constitution of, 1820.
containing the 2-chloroethyl group, 2177.
*di***Sulphides**, aliphatic, physical properties and constitution of, 1820.
*poly***Sulphides**, structure of, 322, 1256.
2-Sulphobenzoic acid, 4-nitro-, dimethyl ester, 1616.
2-*p*-Sulphonamidophenylguanidino-6-methylpyrimidine, 4-hydroxy-, 579.
Sulphonation, aromatic, kinetics of, 1065.
2-*p*-Sulphondimethylaminophenylguanidino-6-methylpyrimidine, 4-hydroxy-, 579.
Sulphonyl sulphides, structure of, 322, 1256.
Sulphur *di*oxide, equilibrium of, with ammonia and water, 76.
Sulphuric acid, sulphonation by, in nitrobenzene solution, 1065.
Persulphates, oxidation of phenols by, 2303.
Sulphur vesicants, organic, 35, 38, 42, 44, 47.
Sulphuric acid. See under Sulphur.
Sulphuryl chlorofluoride and fluoride, preparation and reactions of, 2183.
Surfaces, freshly-formed, properties of, 930, 936, 943.
Surface tension, measurement of, vertical-plate method for, 931.
Sweet potato starch. See under Starch.
Sydnones, 2307.
C- and *N*-substituted, dipole moments of, 2269.
Synthesis, asymmetric, 1085.
Systems, anionotropic, rearrangement and substitution in, 1, 4, 8.
olefinic, α-methylenic reactivity in, 89.

T.

Tartaric acid, formation of, by oxidation and hydrolysis of oxycelluloses, 1135.
Tea, green, catechins of, 2249.
Temperature, effect of, on rates and product-proportions in elimination reactions, 2049.
Terpenoids, spectra of, infra-red absorption, 1412.
Terpenoid compounds, spectra of, absorption, 1306.
2:3:5:6-Tetra-acetyl 1:4-anhydrosorbitol, 301.
4-Tetra-acetyl-D-galactofuranosidamino-5-(2′:5′-*di*chlorobenzeneazo)-2-methylthiopyrimidine, 6-amino-, 962.
4-Tetra-acetyl-D-galactopyranosidamino-5-(2′:5′-*di*chlorobenzeneazo)-2-methylthiopyrimidine, 6-amino-, 962.
4-Tetra-acetyl-D-glucopyranosidamino-5-(2′:5′-*di*chlorobenzeneazo)-2-methylthiopyrimidine, 6-amino-, 963.
2-*O*-Tetra-acetyl-β-glucosidoxy-5-methoxybenzoic acid, methyl ester, 2222.
1-Tetra-acetyl-D-mannosidoglyoxaline-4:5-dicarboxyamide, 524.
3-*n*-Tetradecyl-2-*n*-pentadecylcinchoninic acid, 110.
1:2:4:5-Tetradeuterobenzene, spectrum of, absorption, ultraviolet, 475.
3:3′:4:4′-Tetraethoxy-α-azopropylbenzene, 890.
3′:4′:6:7-Tetraethoxy-1-benzyl-3-methyl*iso*quinoline, 889.
3′:4′:6:7-Tetraethoxy-1-phenyl-3-methyl*iso*quinoline, and its hydrochloride, 889.
***NN′N′*-Tetraethylethylenediamine**, *NNN′N′-tetra*-2-chloro-, 2175.
Tetrahydroanhydro-ψ-strychninephosphorous acid, 956.
1:2:3:4-Tetrahydro-11-aza-6:7-acechrysene, and its picrate, 1540.
6:7:8:9-Tetrahydro-2:3-benzacridine, 5-amino-, 5-chloro-, and 5-hydroxy-, 1290.
5:6:7:8-Tetrahydro-1:2-benzphenanthridine, and 9-amino-, 1540.
Tetrahydrodi*chano*strychnidine, and its acetyl derivative, 1665.
Tetrahydrodi*chano*strychnidine, hydroxy-, 1664.
Tetrahydrofuran, amino-, derivatives, 155.
Tetrahydrofurans related to amidone, 1993.
Tetrahydrophenanthridines, synthesis of, 1537.
5:6:7:8-Tetrahydrophenanthridine, and 9-amino-, and 3-nitro-, and their derivatives, 1539.
Tetrahydropurpurogallin, 1049.
Tetrahydroquinoline-4-carboxylic acid, 2-hydroxy-, 554.
Tetrahydrorottlerin, synthesis of, 113.
Tetrahydro*allo*rottlerin, synthesis of, 113.
2:2:5:5-Tetrakischloromethylpiperazine, and its derivatives, 1905.
2:3:5:6-Tetrakismethanesulphonyl 1:4-anhydrosorbitol, 301.
2:3:4:6-Tetrakismethanesulphonyl styracitol, 2207.
Tetralin, autoxidation of, 1574, 1578, 1585.
hydroperoxide, decomposition of, 1578.
4:2′:3′:4′-Tetramethoxybenz*cyclo*heptene, 1049.
4:2′:3′:4′-Tetramethoxybenz*cyclo*hepten-3-ol, and its 3:5-dinitrobenzoate, 1050.
4:2′:3′:4′-Tetramethoxybenz*cyclo*hepten-3-one, and its 2:4-dinitrophenylhydrazone, 1049.
5:6:5′:6′-Tetramethoxyindigo, 1246.
5:6:5′:6′-Tetra(methoxymethoxy)indigo, 1246.
4:7:2′:4′-Tetramethoxy-3-phenylcoumarin, 175.
2:2:3:3-Tetramethylbutanal 2:4-*di*nitrophenylhydrazone, 286.
semicarbazone, 1333.
αaββ-Tetramethyl-*n*-butyric acid, 1336.
2:2:5:5-Tetramethyl-3:6-di-*tert.*-butyl-1:4-dioxan, and its dinitrophenylhydrazone, 1383.
5:6:9:10-Tetramethyldihydro-1:2-benzanthracene, *di*hydroxy-, and its diacetate, 172.
2:2:6:6-Tetramethyl-4-ethynylpiperidine, 4-hydroxy-, 807.
Tetramethyl hexahydropurpurogallin. See 4:2′:3′:4′-Tetramethoxybenz*cyclo*hepten-3-ol.
Tetramethyl purpurogallin, 120, 1049.
Tetramethyl tetrahydropurpurogallin. See 4:2′:3′:4′-Tetramethoxybenz*cyclo*hepten-3-one.
6:12:18:24-Tetraoxa-3:9:15:21:27-pentathianonacosane, 1:29-*di*chloro-, and its derivatives, 44.
Tetraphenylglycol, complexes of, with pyridinium salts, 385.
ωωω′ω′-Tetraphenyl-*p*-xylylene glycol, complexes of, with pyridinium salts, 385.
2:6′-Tetraquinolyl, 2011.
Thallium, reaction of, with nitrosyl chloride, 1957.
Thallous salts, reaction of, with nitrosyl chloride, 1957.
Thallium determination:—
determination of, 1957.
Thermochemistry of solutions, 1016, 1019.
Thiadiazole ring, 870.
Thiazole, 2:5-*di*amino-, derivatives of, 1265.
2-benzoyl derivative, and its salts, 1264, 1265.
5-amino-2-mercapto-, and its acetyl derivative, 205.
2-mercapto-, Schiff's base from, 204.
Thiazole-4-carboxylic acid, 2:5-*di*amino-, 2-benzoyl derivative, and its ethyl ester, 1343.
ethyl ester, derivatives of, 1343.
Thiazolidine–butyroazlactone rings, synthesis of, 1919.
Thiazolones, preparation of, 1056.
Thiazol-5-one, 2-mercapto-, and its acetyl derivative, 204.
2-(2′-Thienyl)-Δ³-pyrroline, and its picrate, 187.
2- and 3-Thienylthioacetic acids, and their derivatives, 769.
Thioanisole, 4-nitro-2-amino-, preparation of, 873.
Thioanisyl-2-azo-β-naphthol, 4-nitro-, 873.
Thioaryloxides, nitro-, reaction of, with polynitro-aromatic compounds, 2017.
***N*-Thiocarbobenzyloxyglycine**, and its derivatives, 1059.
4-Thiocarboxy-5-phenyl-2-thiothiazolidone, and its derivatives, 1064.
2-Thio-3-chloromethylbenzthiazolone, 1717.
***iso*Thiocyanates**, reaction of, with α-amino-nitriles, 1262.
Thiocyanatophosphonic acid, diethyl ester, 701.
Thiocyanic acid, alkyl esters, preparation and physical properties of, 1848.
3-chloroallyl ester, 2182.
Thiodiglycol, preparation of, 1892.
2-Thio-4-(*p*-dimethylaminostyryl)uracil, 1715.
Thio-esters, hydrolysis of, 1549.
Thioethylene glycol, preparation of, 1892.
5-Thioformamido-4-D-glucosidamino-2-methylthiopyrimidine, 6-amino-, and its 4-tetra-acetyl derivative, 966.
2-Thio-3-hydroxymethylbenzthiazolone, 1717.
Thiols, aliphatic, physical properties and constitution of, 1820.
Thiol-compounds, addition of, to double bonds, 1683.
Thionaphthen, derivatives of, 1615.
detoxication of, as catalyst poison, 1916.
1:3-oxazine derivatives of, 78.
Thionaphthens, formation of, from phenylthioacetic acid derivatives, 81.
3-Thionaphthen-2-carboxylic acid, 3-hydroxy-, 3-acetyl derivative, ethyl ester, 84.
Thionaphthen sulphone, acetoxymercuri-derivative, 1617.
Thionaphthen sulphone, nitro-, *di*bromide, 1616.
Thiophen, detoxication of, 1091.
Thiophen-2-sulphonamide, 4-amino-, and 4- and 5-nitro-, 527.
Thiophen-2-sulphonic acid, *m*-methoxyphenyl ester, 526.
Thiophen-2-sulphonyl chloride, nitration of, 525.
Thiophen-2-sulphonyl chloride, 4-nitro-, 527.
1-Thiophenyl acetate, 4-nitro-2-amino-, 2-acetyl derivative, 873.
Thiophthens, isomeric, detoxication of, as catalyst poisons, 1916.
2-Thio-3-piperidinomethylbenzthiazolone, 1717.
2-Thiothiazolidone-4-carboxylic acid, 1339.
Thioureas, formation of, by reduction with Raney nickel, 1716.
Thorium oxide, catalytic, preparation of, 612.
DL-Threonine, synthesis of, 310.
Thymol as fractionating agent for starch, 1687.
Thymus nucleic acid, sedimentation of, in the ultracentrifuge, 1382.
Titanium nitride, deposition and growth of, on hot filaments, 1709.
Toluene, methylation of, by dimethyl ether, 2154.
Toluene, 2:4:6-*tri*amino-, triacetyl derivative, 114.
fluoro-derivatives, spectra of, infra-red absorption, 1434.
2:5-*di*hydroxy-, 2-benzyl derivative, 2307.
2:4:6-*tri*nitro-, derivatives of, 1612.
reduction of, 1275.
6-nitro-2-hydroxy-, 2-benzyl derivative, 1609.
5-*p*-Tolueneazoquinoline, 6-amino-, 223.
***p*-Toluenesulphinic acid**, ω-amino-, ω-acetyl derivative, preparation of, 148.
***p*-Toluenesulphonamide**, *N*-substituted derivatives, preparation of, 110.
2-*p*-Toluenesulphonamidobenzoic acid, 4-nitro-, methyl ester, 366.

1-Toluene-*p*-sulphonamidopleiadene-7:12-dione, 1757.
***p*-Toluenesulphon-(β-diethylaminoethyl)anilide**, 3-nitro-, and its salts, 1930.
Toluene-*p*-sulphon-2-fluoroethylamide, 2176.
Toluene-*p*-sulphonic acid, 2-fluoroethyl ester, 2176.
2-*p*-Toluenesulphonmethylamidobenzoic acid, 4-nitro-, methyl ester, 366.
3-*p*-Toluenesulphomethylamido-*N*-dimethylaniline hydriodide, 1929.
2-Toluene-*p*-sulphontoluidide, 3:5-*di*nitro-, 2134.
***N'*-*p*-Toluenesulphonyl-*N*-phenylbenzamidine**, 112.
***N'*-*p*-Toluenesulphonyl-*N*-tolylbenzamidines**, 112.
***p*-Toluic acid**, 3-bromo-, 1233.
***m*-Toluidine**, 4-chloro-5-nitro-, 1009.
***p*-Toluidine** hydrochloride, condensation product of, with 2-*p*-toluidinopent-2-en-4-one, 2027.
***p*-Toluidine**, 6-nitro-2:4-*di*amino-, mono-, and di-acetyl derivatives, 1276.
Toluidines, 3-nitro-, benzenesulphonyl derivatives of, 1312.
6-*p*-Toluidino*meso*benzanthrone, 1749.
4-*p*-Toluidino-2-*tert.*-butylanthraquinone, 1-amino-, 1628.
***o*- and *p*-Toluidinomethylenemalonic acids**, diethyl esters, 893.
2-*p*-Toluidinopent-2-en-4-one, condensation product of, with *p*-toluidine hydrochloride, 2027.
***N*-Toluoyl-*p*-toluenesulphonamides**, 111.
β-*p*-Tolylalanine, β-ω-amino-, salts, 87.
***N*-*p*-Tolylbenzimino-*o*-nitrophenyl ether**, *N*-*o*-bromo-, 1604.
***N*-*o*-Tolylbenzimino-8-quinolyl ether**, 1605.
***N*-*p*-Tolylbenzimino-8-quinolyl ether**, *N*-*o*-bromo-, 1605.
***p*-Tolyl α-bromobenzyl ketone**, 866.
***p*-Tolylcarbamic acid**, 3-nitro-, ethyl ester, 878.
***p*-Tolyl-2-carboxyethyl sulphone**, 1595.
***o*-Tolyldicyandiamide**, 1634.
N^1-*p*-Tolyl-N^5-ethyldiguanide hydrochloride, 1635.
2-*p*-Tolyl-1-ethylindole, 854.
3-*p*-Tolyl-1-ethylindole, 855.
***N*-*o*-Tolylglycine**, *N*-3-nitro-, 2133.
***m*-Tolylglycine**, 4-nitro-, 1312.
2-*p*-Tolylindole, and 1-nitroso-, 854.
2-*p*-Tolyl-1-methylindole, 854.
2-*p*-Tolyl-5-methylindole, and 1-nitroso-, 854.
3-*p*-Tolyl-1-methylindole, 855.
1-*p*-Tolyl-7-methylnaphthalene-2:3-dicarboxylic acid, synthesis of, and its anhydride, 1270, 1272.
1-*m*-Tolylnaphthalene-2-carboxylic acid, 1233.
1-*m*-Tolylnaphthalene-4'-carboxylic acid, 1233.
1-*p*-Tolylnaphthalene-2-carboxylic acid, 1234.
1-*p*-Tolylnaphthalene-3'-carboxylic acid, 1234.
***p*-Tolylnaphthylarsonous acids**, 2209.
***p*-Tolylnaphthylcyanoarsines**, 2212.
***m*-Tolyl-α-naphthylmethane**, 4-amino-, and its acetyl derivative, 298.
***p*-Tolyl 2-(2:4:6-*tri*nitrophenyl)ethyl sulphide** and sulphoxide, 1615.
***p*-Tolyl 2-(2:4:6-*tri*nitrophenyl)ethyl sulphone**, 1615.
4-*p*-Tolyloxy-2-methyl-5:6-benzquinoline, 1287.
1-*p*-Tolylphenacylaniline, 867.
hydrobromide, 868.
1-*p*-Tolylphenacyl-*N*-ethylaniline, 867.
1-*p*-Tolylphenacyl-*N*-methylaniline, 867.
N^1-Tolyl-N^5-*iso*propyldiguanides, and their hydrochlorides, 1635.
2-*p*-Tolylpyrrolidine, and its picrate, 187.
2-*p*-Tolyl-Δ^2-pyrroline, and its picrate, 187.
Tolyl-*m*-4-xylylarsonous acids, 2209.
Tolyl-*m*-4-xylylcyanoarsines, 2211.
6-Tosyl 1:4-anhydrosorbitol, 302.
6-Tosyl 3:5-benzylidene 1:4-anhydrosorbitol, 301.
1-*p*-Tosyl-4-phenylpiperidine-4-carboxylic acid, 560.
4-Triacetyl-L-arabofuranosidamino-5-(2':5'-*di*chlorobenzeneazo)-2-methylthiopyrimidine, 6-amino-, 963.
4-Triacetyl-L-arabopyranosidamino-5-(2':5'-*di*chlorobenzeneazo)-2-methylthiopyrimidine, 6-amino-, 964.
1-Triacetyl-D-ribosidoglyoxaline-4:5-dicarboxyamide, 524.
4-Triacetyl-D-xylosidaminopyrimidines, hydrogen bonding in, 2265.
Triallylamine, *tri*-3-chloro-, 2181.
1:3:5-Triazine, 2:4-*di*chloro-6-amino-, 563.
1:3:5-Triazines, substituted, 561.
3:4-Triazolo-6:7-benzquinoline, 1289.
***n*-Tridecane-2-carboxylic acid**, See α-Methyltridecylic acid.
1:3:5-Trideuterobenzene, spectrum of, absorption, ultra-violet, 445.
fluorescence, ultra-violet, 456.
Triethyl trithiophosphate, 1014.
Triethylamine, *tri*-2-bromo-, and its hydrobromide, 2176.
tri-2-chloro-, compounds related to, 2174.
tri-2-fluoro-, 2176.
4-Triethylaminoacetamido-2-methyl-1-naphthol chloride, 185.
Triethyl-lead fluoroacetate, 1779.
Tri(ethylthioethyl)amine, *tri*-2-chloro-, hydrochloride, 2175.
Triglycerides, polymorphism of, 985.
Triketoindane, photochemical reaction of, with stilbene, 2128.
Triketones, symmetrical, action of hydrogen peroxide on, 50.
1:2:3-Triketones, photochemical reactions of, with ethylenes, 2126.
4:2':3'-Trimethoxybenz*cyclo*heptene, 4'-hydroxy-, 1049.
1':2':3-Trimethoxybenz*cyclo*hepten-3-one, and its 2:4-dinitrophenylhydrazone, 1051.
2':3':4'-Trimethoxybenz*cyclo*hepten-3-one, and its 2:4-dinitrophenylhydrazone, 1050.
4:2':3'-Trimethoxybenz*cyclo*hepten-3-one, 4'-hydroxy-, and its derivatives, 120, 1049.
γ-(2:3:4-Trimethoxybenzoyl)butyric acid, 1051.
γ-(3:4:5-Trimethoxybenzoyl)butyric acid, and its esters, 1050.
***N*-3:4:5-Trimethoxybenzoyl-*p*-toluenesulphonamide**, 111.
γ-(2:3:4-Trimethoxy-6-carboxyphenyl)butyric acid, 1051.
γ-(3:4:5-Trimethoxy-2-carboxyphenyl)butyric acid, and its dimethyl ester, 1050.
2:3:2'-Trimethoxy-5:4'-divinyldiphenyl ether-6:5'-dialdehyde, 2173.
7:2':4'-Trimethoxy-3-phenylcoumarin, 4-hydroxy-, and its *O*-acetyl derivative, 175.
7:3':4'-Trimethoxy-3-phenylcoumarin, 4-hydroxy-, and its derivatives, 175.
δ-(2:3:4-Trimethoxyphenyl)valeric acid, 1051.
δ-(3:4:5-Trimethoxyphenyl)valeric acid, 1050.
Trimethoxyphthalide, 120.
***NNN'*-Trimethylacetamidine**, and its benzenesulphonate, 1619.
4-Trimethylaminoacetamido-2-methyl-1-naphthol chloride, 185.
5:9:10-Trimethyldihydro-1:2-benzanthracene, *di*hydroxy-, and its diacetate, 172.
4:4':6-Trimethyl-2:2'-dipyrimidylamine, 6'-chloro-, and 6'-hydroxy-, 596.
1:5:5-Trimethyl-2:4-dithiohydantoin, 1622.
2:3:4-Trimethylfluoranthene, and its derivatives, 1139.
Trimethyl hexahydrodeoxypurpurogallin. See 4:2':3'-Trimethoxybenz*cyclo*heptene, 4'-hydroxy-.
Trimethylhexahydropurpurogallin, 119.
[2-(1:3:3-Trimethylindolenine)][2-(3-ethylbenzselenazole)]-[γβ'-dimethin-2'-(1':3':3'-trimethylindolenine)]trimethincyanine *di*perchlorate, 1883.
[2-(1:3:3-Trimethylindolenine)][2-(3-ethylbenzselenazole)]trimethincyanine *per*chlorate, 1887.
[2-(1:3:3-Trimethylindolenine)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine *per*chlorate, 1884.
[2-(1:3:3-Trimethylindolenine)][2-(3-ethylbenzthiazole)]trimethincyanine iodide, 1887.
[2-(1:3:3-Trimethylindolenine)][3-(4-methyldihydro-β-quinindene)]dimethincyanine, 1897.
2:3:6-Trimethyl D-mannonic acid, phenylhydrazide, 1279.
2:4:4-Trimethylpentanal 2:4-*di*nitrophenylhydrazone, 1329.
2:4:4-Trimethylpentane-1:2-diol, 1329.
2:4:4-Trimethylpentane-2:3-diol, and its nitrobenzoate, 286.
2:4:4-Trimethylpentane-1:2- and -2:3-diol *di*acetates, 1333.
2:4:4-Trimethylpentan-3-ol, and its derivatives, 287.
2:4:4-Trimethylpent-1-ene. See α-Di*iso*butylene.
2:4:4-Trimethylpent-2-ene. See β-Di*iso*butylene.
2:4:4-Trimethylpent-1-en-3-ol, and its derivatives, 287.
2:4:4-Trimethylpent-2-en-1-ol, and its nitrobenzoates, 1333.
Trimethyl purpurogallin, 1049.
Trimethyl D-ribofuranose, characterisation of, 2035.
2:3:5-Trimethyl D-ribonolactone, 2037.
2:3:5-Trimethyl D-ribonophenylhydrazide, 2037.
2:3:5-Trimethyl D-ribose anilide, 2036.
Trimethyl tetrahydropurpurogallin. See 4:2':3'-Trimethoxybenz*cyclo*hepten-3-one, 4'-hydroxy-.
3:3':3-Trimethylthiacarbocyanine iodide, 689.
3:4:4-Trimethylthiazolidine-2-thione, 5-imino-, and its derivatives, 1621.

3:4:4-Trimethylthiazolid-5-one-2-thione, 1621.
αγγ-Trimethyl-*n*-valeric acid, ethyl ester, 1336.
6:12:18-Trioxa-3:9:15:21-tetrathiatricosane, 1:23-*di*chloro-, and 1:23-*di*hydroxy-, and their derivatives, 43.
Triphenylethylene, and its derivatives, substitution reactions of, 1078.
Triphenylethylene series, œstrogens of, 150.
Triphenylmethane, oxidation of, by chromic acid, 1670.
Triphenylmethyl radical, cationoid reactivity of, compared with anionic reactivity of desyl and α-benzoylbenzhydryl radicals, 1549.
α-Triphenylmethylthioacetic acid, ethyl ester, 1551.
2:6′-Triquinolyl, 2010.
Trisaminomethylaminomethane, and its salts, 1905.
Tris(carbethoxyaminomethyl)carbethoxyaminomethane, 1906.
Trischloromethylaminomethane, and its *N*-*m*-nitrobenzylidene derivative, 1904.
Trischloromethylnitromethane, 1904.
Trischloromethyltoluene-*p*-sulphonamidomethane, 1905.
Tris-4-cyanobutylmethane, nitro-, 230.
Trishydroxymethylnitromethane, derivatives, 1902.
Tris-4:4′:4″-methylnitroaminotriphenylcarbinol, 3:5:3′:5′:3″:5″-*hexa*nitro-, 2170.
Tris(toluene-*p*-sulphonamidomethyl)toluene-*p*-sulphonamidomethane, 1905.
Tris(toluene-*p*-sulphonmethylamidomethyl)toluene-*p*-sulphonamidomethane, 1905.
Trithians, stereochemistry of, 892.
Trypanocides, *N*-heterocyclic, 188.
Tryptophan, aldehyde reactions for, 705.
nuclear-*C*-methylated derivatives, synthesis of, 705.
***d*-Tubocurarine chloride**, 1947.
constitution of, 265.

U.

Ullmann reaction, preparation of *s*-dinitrodiphenyls by, 264.
Undecane, 1:6:11-*tri*amino-, tripicrate, 231.
***n*-Undecane-2-carboxylic acid**. See α-Methylundecylic acid.
***n*-Undecane-6-carboxylic acid**. See α-*n*-Amyloenanthic acid.
***n*-Undecane-1:11-dicarboxylic acid**. See Brassylic acid.
Undecoic acid, α-amino-, 1388.
Undecylenic acid, esters, 662.
Unsaturated compounds, conjugated, addition to, 17.
kinetics of halogen addition to, 980.
reactions of, 284, 1328, 1331, 1334.
2-Ureido-4:5-dimethoxybenzoic acid, 1764.
2-Ureido-4-methoxybenzamide, 1764.
2-Ureido-6-methoxybenzamide, 1763.
3-Ureido-*p*-tolunitrile, 1763.
Urethanes, preparation of, and conversion into *N*-nitroso-derivatives, 2320.
Uridine, preparation of, from yeast ribonucleic acid, 1936.

V.

Valency, modern theory of, 1461.
***iso*Valeric acid**, β-mercapto-, 1685.
Vanillin, 2-nitro-, derivatives of, 376.
***iso*Vanillin**, 2-nitro-, derivatives of, 376.
Vapour pressure of associated liquids, relation of, to viscosity, 1349.
Veratraldehyde, derivative from, with *cyclo*hexa-1:3-dione, 1372.
Veratraldehyde, 2-nitro-, derivatives of, 376.
***N*-Veratroyl-*p*-toluenesulphonamide**, 111.
Vesicants, 2177, 2180.
sulphur organic, 35, 38, 42, 44, 47.
Vinyl compounds, polymers, cross-linking of, by Friedel-Crafts catalysts, 771.
halides, thermodynamic functions of, 1931.
***cis*- and *trans*-Vinylarsine** oxide, 2-chloro-, 1205.
***cis*- and *trans*-Vinylarsonic acids**, 2-chloro-, 1204.
Vinyl*di*chloroarsines, 2-chloro-, isomeric, 1203, 1206.
***cis*-Vinyl*di*chloroarsine**, 2-chloro-, physicochemical properties of, 1209.
Viscosity, molecular association and, 1345, 1349.
Visnagin, partial synthesis of, 2260.
***iso*Visnagin**, synthesis of, 2260.
***iso*Visnagone**, and its 2:4-dinitrophenylhydrazone, 2263.
Vitamin-*A*, chemistry of, 386.

W.

Walden inversion and steroids, 1032, 1043.
Water, solvating properties of, 1976.
vapour, adsorption of, on proteins, 1083.
Wolff rearrangement, 1674.
Wood, " insoluble red," chemistry of, 174.

X.

Xanthic acid, alkyl esters, and their potassium salts, 1848.
Xylenes, methylation of, by dimethyl ether, 2154.
***m*-2- and -5-Xylenols**, halogenation of, 209.
***m*-2-Xylenol**, 4:5:6-*tri*bromo-, bromide and chloride, 370.
chlorobromo-derivatives, 211.
5-hydroxy-, 5-benzyl derivative, 2306.
***m*-5-Xylenol**, 2:4:6-*tri*chloro-, bromide, 370.
chlorobromo-derivatives, 210.
***m*-Xyloquinone**, 4-chloro-6-bromo-, 211.
***N*-*m*-4-Xylylbenzimino-8-quinolyl ether**, *N*-5-bromo-, 1605.
1-*m*-5′-Xylylnaphthalene-2-carboxylic acid, 1232.
1-*m*-5′-Xylylnaphthalene-4′-carboxylic acid, 1233.

Y.

Yeast ribonucleic acid, constitution of, 1527, 1532.
uridine from, 1936.

Z.

Zeolites, gas-absorption by, 133.
mineral resembling, with chabazite-like sorptive properties, 127.
Zinc iodide, activity coefficients of, 216.
Zinc soaps, solubility of, in organic solvents, 1750.

PUBLICATIONS OF THE SOCIETY

With the exception of certain issues which are out of print, the following may be obtained from the General Secretary:

Journal and Proceedings.		Price to Fellows £ s. d.	Price to Public £ s. d.
Memoirs and Proceedings, 1841–1847 (3 vols.)	per vol.	2 15 0	3 15 0
Quarterly Journal, 1848–1861 (14 vols.)	per vol.	2 15 0	3 15 0
Journal, 1862–1870	per vol.	2 15 0	3 15 0
„ (including Abstracts), 1871–1923	per vol.	2 15 0	3 15 0
„ 1924–1948	per part	5 6	7 6
„ 1949	per vol.	2 15 0	5 0 0
	per part	5 6	10 0
Journal Annual Index, 1871–1948	per copy	5 6	7 6
Journal Collective Index, Vol. I, 1841–1872	per vol.	2 0	2 0*
„ „ „ Vol. II, 1873–1882	per vol.	5 0	5 0*
„ „ „ Vol. III, 1883–1892	per vol.	7 6	7 6*
„ „ „ Vol. IV, 1893–1902	per vol.	10 0	10 0*
„ „ „ Vol. V, 1903–1912	per vol.	2 0 0	2 10 0*
„ „ „ Vol. VI, 1913–1922	per vol.	3 5 0	5 0 0*
†Proceedings, 1885–1914	per vol.	7 6	7 6*
„ „	per part	6	6*

Annual Reports on the Progress of Chemistry.			
Vol. I (1904)—Vol. XLII (1945)	per copy	8 6	15 0
Vol. XLIII (1946)	per copy	8 6	1 0 0
Vol. XLIV (1947)—Vol. XLV (1948)	per copy	12 6	1 0 0

Quarterly Reviews.			
Vol. I (1947)—Vol. III (1949)	per vol.	15 0	1 5 0
„	per part	5 0	8 0

Other Publications.		
The Chemical Society, 1841—1941 (A Historical Review by T. S. Moore and J. C. Philip)	7 6	12 6
British Chemists (Edited by A. Findlay and W. H. Mills)	12 6	18 0
Record of the Centenary Celebrations	5 0	5 0
Jubilee Volume (History of the Chemical Society from 1841 to 1891)	2 6	2 6*
Memorial Lectures, Vol. I, 1893–1900	9 0	10 6*
„ „ Vol. II, 1901–1913	7 0	8 0*
„ „ Vol. III, 1914–1932	5 0	6 0*
Volume of Faraday Lectures, 1869 to 1928	5 6	8 6*
Portraits of Eminent Chemists, set of 8	18 0	1 2 0*
„ „ „ each	2 6	3 0*
(The set includes portraits of Bunsen, Fischer, Hofmann, Mendeleef, Pasteur, Perkin, Ramsay, and Roscoe. Each portrait measures 8″ × 6″. Size of mount 15″ × 11″.)		
Table of International Atomic Weights, 1947	per copy	9	9

* *Postage extra. All other publications post free.*

† *Included with Journal as from January*, 1915.

ABSTRACTS

As from January, 1924, the Abstracts were separated from the Journal of the Chemical Society and published independently.

			Price to Fellows £ s. d.	Price to Public £ s. d.
A. Abstracts.				
1924–36	British Chemical Abstracts "A" (Pure Chemistry) ...	per vol.	2 15 0	3 15 0
" " " " " " ...		per part	5 6	7 6
1937–44	British Chemical and Physiological Abstracts "A", and			
†1945–46	British Abstracts "A":			
	A. I (General, Physical, and Inorganic Chemistry)...	per annum	1 0 0	2 15 0*
		per part	2 0	5 0
	A. II (Organic Chemistry)	per annum	1 0 6	2 15 0*
		per part	2 0	5 0
	A. III (Physiology and Biochemistry)	per annum	1 12 0	4 0 0*
		per part	3 6	7 6
	A. I, A. II, and A. III together	per annum	3 5 0	8 0 0*
		per part	7 6	17 6
†1947	British Abstracts "A":			
	A. I (General, Physical, and Inorganic Chemistry)...	per annum	1 5 0	2 15 0*
		per part	2 6	5 0
	A. II (Organic Chemistry)	per annum	1 10 0	2 15 0*
		per part	3 0	5 0
	A. III (Physiology and Biochemistry)	per annum	2 0 0	4 0 0*
		per part	5 0	7 6
	A. I, A. II, and A. III together	per annum	4 15 0	8 0 0*
		per part	10 6	17 6
†1948–49	British Abstracts "A":			
	A. I (General, Physical, and Inorganic Chemistry)...	per annum	1 5 0	2 15 0*
		per part	2 6	5 6
	A. II (Organic Chemistry)	per annum	1 10 0	3 10 0*
		per part	3 0	7 0
	A. III (Physiology and Biochemistry)	per annum	2 0 0	4 5 0*
		per part	5 0	8 6
	A. I, A. II, and A. III together.....	per annum	4 15 0	9 0 0*
		per part	10 6	1 1 0
C. Abstracts.				
1944	British Chemical and Physiological Abstracts "C," and			
†1945–46	British Abstracts "C" (Apparatus and Analysis)	per annum	5 0	15 0
		per part	1 6	4 6
†1947	British Abstracts "C" (Apparatus and Analysis)	per annum	7 6	15 0
		per part	1 6	4 6
†1948–49	British Abstracts "C" (Apparatus and Analysis)	per annum	7 6	2 0 0
		per part	1 6	7 0
Annual Indexes.				
1924–36	Annual Index to British Chemical Abstracts "A".....	per copy	7 0	11 0
1937–38	Annual Index to British Chemical and Physiological Abstracts "A" and "B" (combined)	per copy	10 6	15 0
1939–43	Annual Index to British Chemical and Physiological Abstracts "A"	per copy	10 6	12 6
1944	Annual Index to British Chemical and Physiological Abstracts "A" and "C" (combined)	per copy	10 6	12 6
†1945–47	Annual Index to British Abstracts "A" and "C" (combined)	per copy	10 6	12 6
†1948	Annual Index to British Abstracts "A", "B", and "C" (combined)	per copy	10 6	1 0 0
1944	Annual Index to British Chemical and Physiological Abstracts "C"	per copy	2 0	4 6
†1945–46	Annual Index to British Abstracts "C"	per copy	2 0	4 6
†1947	Annual Index to British Abstracts "C"	per copy	3 0	4 6
Collective Indexes.				
†1923–32	Decennial Index of British Chemical Abstracts "A" and "B" (combined)	per copy	4 0 0	10 0 0
†1933–37	Quinquennial Index of British Chemical Abstracts "A" and "B" (combined)	per copy	4 0 0	10 0 0

* *Including one copy of the Index.*

† *Obtainable by the public from the Bureau of Abstracts, 9/10, Savile Row, London, W. 1.*